09-04-02

Practitioner's Docket No. INS-31061-A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant	:	Alan R. Hirsch
Serial No.	:	09/707,655
Filing Date	:	November 7, 2000
For	:	Use of Odorants to Alter Blood Flow to the Vagina, and Article of Manufacture Therefor
Group Art Unit:		1651
Examiner	:	C. Tate
Docket No.:		INS-31061-A

CERTIFICATION UNDER 37 CFR 1.8(a) and 1.10

I hereby certify that, on the date shown below, this correspondence is being:

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Date: September 3, 2002 Kristine M Strodthoff

Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF APPEAL BRIEF (PATENT APPLICATION-37 C.F.R. 1.192)

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on July 1, 2002.

2. STATUS OF APPLICANT

The Applicant/Appellant is a small entity.

3. FEE FOR FILING APPEAL BRIEF

Pursuant to 37 C.F.R. 1.17(c), the fee for filing the Appeal Brief is:

Small entity	$160.00
Appeal Brief fee due	**$ 160.00**

4. EXTENSION OF TERM

The proceedings herein are for a patent application and the provisions of 37 C.F.R.section 1.136 apply.

Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

5. TOTAL FEE DUE

The total fee due is:

Appeal brief fee	$ 160.00
Extension fee (if any)	$ 0.00
TOTAL FEE DUE	**$ 160.00**

6. FEE PAYMENT

Attached is a check in the sum of $ 160.00.

7. FEE DEFICIENCY

If any additional extension and/or fee is required, this is a request therefor and to charge Account No. 232053. If any additional fee for claims is required, charge Account No. 232053.

Date: September 3, 2002

Kristine M Strodthoff
Signature of Practitioner

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PATENT

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant : Alan R. Hirsch

Serial No. : 09/707,655

Filing Date : November 7, 2000

For : USE OF ODORANTS TO ALTER BLOOD FLOW TO THE VAGINA, AND ARTICLE OF MANUFACTURE THEREFOR

Group Art Unit: 1651

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Date: September 3, 2002 Kristine M Strodthoff

Assistant Commissioner for Patents
Washington, D.C. 20231

APPELLANT'S BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

Sir:

This is an appeal from the final rejection of Claims 24-33, 35, 36, 38, 41, 42 and 44-46 of the above-identified application, as set forth in the Office Action mailed April 10, 2002. The Notice of Appeal was timely filed on July 1, 2002.

I. REAL PARTY IN INTEREST

The real party in interest is Alan R. Hirsch.

II. RELATED APPEALS AND INTERFERENCES

There are no related applications currently either under appeal or the subject of an interference proceeding. A related application USSN 09/211,507 is currently under final rejection.

III. STATUS OF CLAIMS

Claims 24-33, 35, 36, 38, 41, 42 and 44-46 are pending and the subject of this Appeal. The pending claims are provided in the attached Appendix.

IV. STATUS OF AMENDMENTS

Subsequent to final rejection, a Response under 37 C.F.R. §1.116 was filed on June 10, 2002. No amendments to the claims were made in the Response.

V. SUMMARY OF THE INVENTION

Appellant's invention relates to altering blood flow to the vagina of a female individual by the inhalation of an odorant. The claims are directed to articles comprising a unit dosage amount of the odorant and instructions for administering the odorant to alter blood flow to the vagina.

Claim 24 and dependent Claims 26-33, 36 and 38 are directed to an article comprising particular odorant mixtures: licorice-based and banana nut bread odorants, licorice-based and cucumber odorants, lavender and pumpkin pie odorants, and baby powder and chocolate odorants.

Claim 25 is directed to an article comprising an odorant and instructions, and a device for measuring blood flow to the vagina of the female individual, and/or means for testing olfactory ability in the female individual.

Claim 35 is directed to an article comprising a mixture of a licorice-based odorant and a cucumber odorant.

Claim 41 and dependent Claims 42 and 44 are directed to an article comprising particular odorant mixtures: licorice-based and cucumber odorants, lavender and pumpkin pie odorants, and baby powder and chocolate odorants.

Claim 45 and dependent Claim 46 are directed to an article comprising a mixture of a licorice-based odorant and a cucumber odorant.

The articles (kits) are described more fully in the detailed description of the invention at page 7, lines 3-23. Odorants are described at page 4, lines 9-29, and the Example at page 12, listing commercial sources of the odorants.

Screening of odorants for effectiveness in altering blood flow to the vagina is addressed at pages 7-8, and the Example at pages 8-16. As described in the Example at page 9, a vaginal process graphic recording device, a photophlethysmograph, can be utilized to monitor change in blood flow to the vagina.

The Example at pages 8-16 provides a working example of the application of the odorants recited in the claims to female individuals, and procedures used in assessing the effectiveness of the odorants to alter blood flow to the vagina.

VI. ISSUES PRESENTED FOR REVIEW

1. Whether Claims 24-33, 35, 36, 38, 41, 42 and 44-46 are unpatentable under 35 U.S.C. § 112, first paragraph, for failing to adequately teach how to make and/or use the invention, i.e., for failing to provide an enabling disclosure.

2. Whether Claims 24-33, 35, 36, 38, 41, 42 and 44-46 are unpatentable under 35 U.S.C. § 112, second paragraph, for indefinite claim language.

More specifically, the issue to be decided in this appeal is whether or not Appellant is required to limit the odorants recited in the claims to the specific commercial sources of the odorants disclosed in the Example.

VII. GROUPING OF CLAIMS

For the purposes of this appeal, and in the arguments below, Claims 24, 26-33, 35, 36 and 38, 41, 42 and 44-46 are grouped and stand together, and Claim 25 is grouped and stands together.

VIII. ARGUMENT

A. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

In the final Office Action mailed April 10, 2002, and the Advisory Action mailed June 21, 2002, responding to Appellant's Response mailed June 10, 2002, the Examiner rejected Claims 24-33, 35, 36, 38, 41, 42 and 44-46 under 35 U.S.C. § 112, first paragraph, stating that Appellant fails to adequately teach the mixtures of odorants claimed, i.e., fails to provide an enabling disclosure. Appellant respectfully requests reversal of this rejection of the claims.

During the prosecution of the present application and its parent, USSN 09/211,507 (pending), the Examiner has maintained this same position concerning the adequacy of the disclosure.

In the Office Action mailed October 24, 2001, and again in the final Office Action mailed April 10, 2002, the Examiner stated that the claims are enabled only for "the instantly disclosed particular commercial odorants and mixtures thereof" — not for "undefined and/or non-commercial odorants thereof." The Examiner maintained this position stating that "it would take undue experimentation without a reasonable expectation of success for one of skill in the art to prepare and use an article of manufacture having the unusual disclosed/claimed functional effect, other than using one of the particular demonstrated commercial odorants or mixtures thereof..."

1. THE EXAMINER HAS FAILED TO MEET HIS BURDEN OF SHOWING THAT THE CLAIMS ARE NOT ENABLED AND REQUIRE UNDUE EXPERIMENTATION.

The Examiner has the burden of giving reasons, supported by the record as a whole, why the specification is not enabling and requires undue experimentation. *In re Angtadt and Griffin*, 190 USPQ 214, 219, 537 F.2d 498, 504 (CCPA 1976).

The Examiner has admitted that the specification is enabling for altering blood flow to the vagina by inhaling "the particular commercial odorants...or mixtures thereof instantly demonstrated," disclosed at page 12, lines 1-13.

However, the Examiner denies the enablement of Applicant's inventive article of manufacture based on an "unusual disclosed functional effect" and an "unusual use" and

characterizes the disclosed odorants/odorant mixtures as being "undefined." The Examiner maintains that the claims are not enabled and require undue experimentation, and requires that the claims be limited to the particular listed commercial odorants or mixtures on the basis of undue experimentation to prepare and use an article of manufacture other than with one of the particular demonstrated commercial odorants. Office Action mailed April 10, 2002, at pages 3-4.

The Examiner has provided no good basis for his position.

First of all, the Examiner erroneously contends that the claims encompass "*any undefined odorant* and/or the various mixture of *subjective odorants*" (emphasis added).

The pending Claims 24, 26-33, 35, 36, 38, 41, 42 and 44-46 are directed to an article comprising *specified mixtures of odorants*.

Claims 24, 26-33, 36, 38: a licorice-based odorant and banana nut bread odorant mixture, a licorice-based odorant and cucumber odorant mixture, a lavender odorant and pumpkin pie odorant mixture, and a baby powder odorant and chocolate odorant mixture.

Claims 41, 42, 44: a licorice-based odorant and cucumber odorant mixture, a lavender odorant and pumpkin pie odorant mixture, and a baby powder odorant and chocolate odorant mixture.

Claims 35, 45, 46: a licorice-based odorant and cucumber odorant mixture.

The Examiner merely asserts that the instantly claimed odorants are highly subjective with respect to the actual odors being encompassed, stating that a given recipe of pumpkin pie or banana nut bread varies according to the ingredients, baby powder varies by commercial manufacturer, cucumber varies based upon the brand, species, age/ripeness, geographic location in which it is grown, etc., licorice-based odorants such as Good and Plenty™ have a distinct odor from that of some other licorice based products such as anise, and chocolate such as milk chocolate has a distinct odor from dark chocolate.

As further support, the Examiner asserts that the use of other odorants would be highly unpredictable between females and should be limited to the commercially identified odorants because the same mixture of odorants can cause an increased blood flow to the vagina in some females and a decreased blood flow to the vagina in other females. The Examiner also cites to

Doty (Philadelphia Sensorics, 1983) to show that variables such as occupation, general health, psychological state and age, make the use of other odorants highly unpredictable between females.

The Examiner has not denied the patentability of the claims based on differing effects. Rather, the Examiner contends that the claims should be limited to the particular disclosed commercial forms of the odorants.

One of ordinary skill in the odorant arts would readily ascertain particular odorants that fall within the scope of the claim other than the particular demonstrated commercial odorant mixtures. Indeed, one of ordinary skill in the odorant arts would be able to ascertain whether a substance had a chocolate aroma, a licorice aroma, a banana nut bread aroma, a cucumber aroma, a lavender aroma, or a baby powder aroma, regardless of whether the substance was the commercial source disclosed, or another synthetic or natural source.

The character of the particular odorants recited in the claims is well-delineated, commercial source odorants are identified, and a working example is provided that would enable an art worker to obtain and employ such compounds as broadly as they are claimed, particularly based on the knowledge in the odorant arts. Clearly, one of ordinary skill in the odorant arts would be fully enabled to practice Appellant's invention utilizing both synthetic and natural odorant mixtures from a variety of sources.

Furthermore, the Examiner assertions based on Doty are without any basis.

Doty (Philadelphia Sensorics, 1983) discloses a test for identifying odorants (the "Smell Identification Test), in which a subject inhales an odorant and then attempts to identify it. Doty described a series of experiments to develop the identification test. In experiment 2, a subject was required to identify 50 stimulants. A series of multiple regression analyses were performed on the data to determine the influence of age, gender, race and smoking habits on the odor identification test scores. The results were then interpreted within the context of the individual's occupation, general health, and psychological state. Age and gender were considered as related to the diminishment of an individual's ability to smell over time.

Doty merely provides information related to a person's ability to smell and to identify odors — *not* to any physiological effect of odors.

The Examiner's assertion that the use of odorants other than the particular commercially identified odorants would be highly unpredictable between females based on Doty's disclosure is clearly unsupported.

The Examiner has not provided any acceptable evidence or reasoning to believe that other sources of the recited odorant mixtures will not also provide useful odorant mixtures as described in the specification. Appellant respectfully submit that the Examiner has not complied with his duty to provide a basis to support this statement that the specification is not enabling as to the generic claims.

As for Claim 25, the Examiner asserts the claim recites an "undefined odorant." Claim 25 recites an article comprising *an odorant to alter blood flow to the vagina*, instructions, with the additional limitations of a device for measuring blood flow to the vagina of the female individual, and/or means for testing olfactory ability in the female individual. The specification is fully enabling for various odorants and odorant mixtures with the demonstrated effect of altering blood flow to the vagina. One skilled in the art would readily identify such odorants other than the commercial sources disclosed based on Appellant's disclosure, including the working example.

One skilled in the odorant arts would be fully enabled to practice Appellant's invention as recited in Claim 25 utilizing a variety of odorants and odorant mixtures, and both synthetic and natural forms of odorants from a variety of sources. However, although Appellant believes Claim 25 as presently pending is clear in its meaning and satisfies the requirements of Section 112, Appellant would consider amending the claim to specific mixtures of odorants in line with pending Claim 24.

The Examiner has provided no persuasive reason why the specification does not enable one skilled in the art to utilize other sources of the recited odorants and practice the invention as broadly as claimed. Absent such a showing, Appellant's claims should be allowed as sufficiently supported by the specification.

2. APPELLANT HAS PROVIDED A SUFFICIENTLY ENABLING DISCLOSURE TO MEET THE REQUIREMENTS OF 35 U.S.C. 112, FIRST PARAGRAPH.

As stated by the U.S. Court of Customs and Patent Appeals in *In re Borkowski*, 164 USPQ 642, 646, 422 F.2d 904, 910 (CCPA 1970), "there is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'" As further stated by the CCPA, "[t]he sufficiency of the disclosure depends not on the number but rather on the nature of the claimed compounds per se and the nature of the supporting disclosures." *In re Cavallito*, 127 USPQ 206, 207, 282 F.2d 363, 367 (CCPA 1960).

According to Section 112, an Applicant is required to teach how to use an invention, and it is well settled that it is not necessary that the specification disclose every operative example when one skilled in the art is fully apprised by the disclosure of what the invention is and how to use it. A disclosure that contains representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope of the claim will possess the described utility is all that is required. The nature of the recited odorants is not ambiguous to one skilled in the odorants arts and would be readily ascertainable.

The claims are limited to odorants that alter blood flow to the vagina and thus do not call for just any odorant. Appellant's disclosure provides reasonable assurance to one skilled in the art that odorant mixtures other than the disclosed commercial sources of the odorants will possess the indicated utility and provide the stated effect. That is, Appellant's submit that the specification is sufficiently enabling for one of ordinary skill in the art to make and use the invention disclosed and claimed without undue experimentation.

Appellant has provided sources of commercial odorants, which are exemplary, from which one skilled in the odorant arts would be able to readily identify suitable odorants from other sources - both synthetic (e.g., commercially or noncommercially prepared) and natural sources (e.g., essential oils) — that have the odorant characteristic to formulate the recited odorant mixture to achieve the desired effect to alter blood flow to the vagina when inhaled by a female individual.

It is well known in the art to utilize such methods as gas chromatography -mass spectrometry (GC-MS), among others, to determine the aroma components of an odorant

compound. A gas chromatograph distinguishes compounds by comparing to a reference standard.

Appellant in his Response filed on June 10, 2002, submitted publications (Abstracts) that address the identification of aroma components that contribute to various odorants:

Jordan et al., "Aromatic profile of aqueous banana essence and banana fruit by gas chromatography-mass spectrometry (GC-MS) and gas chromatography-olfactometry (GC-O)," *J. Agric. Food Chem. 49(10):4813-7 (2001)*;

Zhou et al., Identification and quantification of aroma-active components that contribute to the distinct malty flavor of buckwheat honey," *J. Agric. Food Chem. 50(7): 2016-21 (2002).*

Hamilton et al., "Measuring Farmstead Odors," Oklahoma Cooperative Extension Service, OSU Extension Facts F-1740 (06-1999), at (http://agweb.okstate.edu/pearl/biosystems/general/fl740.htm) : use of a gas chromatograph with a mass spectrometer detector in odorant analysis.

Kirk-Othmer Concise Encyclopedia of Chemical Technology, John Wiley & Sons, Inc. (1985) at page 844 : use of instrumental techniques to separate and identify volatile organic substances, for example, capillary gas chromatography columns in tandem with a mass spectrometer, Fourier transform nmr spectrosopy.

Those of ordinary skill in the art of odor science would readily utilize such known and used instruments as a gas chromatograph with a mass spectrometer detector to identify and/or prepare an odorant as recited in the claims according to an established quality — which in the present application can be ascertained, for example, by utilizing the described commercial source odorants as a comparison. The particular odor ingredients of such odorants mixtures would not vary significantly as the Examiner contends, but would possess a particular "accord" (or "theme") based on particular "notes" according to the particular odorant – as utilized by one of ordinary skill *in the odorant arts*.

The characteristics of the odorants in the mixtures recited in the claims are well understood in the odorant arts, and one skilled in the odorant arts would readily ascertain and provide suitable odorant mixtures from various sources that have the recited odorant character (e.g., mixture of licorice-based and cucumber odorants, etc.) and that would achieve the desired effect of altering blood flow to the vagina when inhaled by a female individual according to Appellant's invention as claimed.

Furthermore, natural sources of the odorants can be utilized in the claimed article. The specification discloses at page 4, lines 16-19, that odorants can be utilized as essential oils—i.e., volatile material isolated from a plant source. Natural sources of odorants are well known in the art and described in various references, for example: *The Merck Index*, 11th Ed., Entry 5261 (lavender) and Entry 4400 (glycyrrhiza), Merck & Co., Inc. (1989); *Remington's Pharmaceutical Sciences*, 18th Ed., Mack Publishing Co., Easton, Pennsylvania (1990) at pages 1294 and 1300; and *Kirk-Othmer Concise Encyclopedia of Chemical Technology*, John Wiley & Sons, Inc. (1985), pages 810-811. Examples of natural sources of the recited odorants include lavender odorant derived from flowers of *Lavandula spica (Ilavandula officinalis or Lavandula vera)* which contain a volatile oil with the principal constituent *l*-linalyl acetate, and licorice odorant derived from the dried rhizome and roots of *Glycyrrhiza glabra* L., *G. glabra* L. var. *glandulifera*, or other varieties.

Appellant has also described screening odorants for effectiveness in altering blood flow to the vagina in the specification at pages 7-8, and in the Example. Screening can be conducted subjectively through interviews with a female subject, or objectively by administering a test to measure initial levels of blood flow to the vagina, re-testing the subject after being given the odorant mixture, and then comparing the results.. As described in the Example at page 9, a vaginal process graphic recording device, a photophlethysmograph, can be utilized to monitor change in blood flow to the vagina.

Appellant has fully described an embodiment of his invention and the manner for ascertaining effectiveness. Sources of the recited odorants other than the particular commercial forms disclosed by Appellant could be readily identified and used to practice the claimed invention without undue experimentation. *United States v. Telectronics, Inc.,* 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied 490 US 1046 (1989).

Satisfaction of the enablement requirement of Section 112 is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." *In re Angstadt and Griffin*, 190 USPQ 214, 219 (CCPA 1976). A considerable amount of experimentation is permissible if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Jackson*, 217 USPQ 804 (Bd. App. 1982).

The character of the particular odorants recited in the claims is well-delineated and a working example is provided. It would be a routine matter for one of ordinary skill to obtain and employ other sources of the recited odorants, and readily determine without undue experimentation whether the odorant works or not.

To require Appellant to limit his claims to only those odorants that are expressly exemplified defeats the purpose of the Patent Laws. Such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of experiments. It would also require an inventor to identify every possible commercial and noncommercial source, and synthetic and natural form of the odorants.

Appellant has provided a sufficiently supporting disclosure, both through the working example and descriptive discussion, to teach those of ordinary skill in the art how to make and use the invention as broadly as it is claimed, and to show that the claimed odorant mixtures are useful in altering blood flow to the vagina of a female individual.

Appellant believes that the present disclosure is fully enabling for odorants other than the particular commercial sources described, and requests that the Examiner withdraw the rejection.

B. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

In the final Office Action mailed April 10, 2002, and the Advisory Action mailed June 21, 2002, responding to Appellant's Response mailed June 10, 2002, the Examiner rejected Claims 24-33, 35, 36, 38, 41, 42 and 44-46 under 35 U.S.C. § 112, second paragraph, stating that Appellant fails to adequately define the metes and bounds of the mixtures of odorants claimed, i.e., fails to use definite claim language. Appellant respectfully requests reversal of this rejection of the claims.

The Examiner has maintained this same position concerning indefiniteness in the parent application, USSN 09/211,507 (pending).

In the Office Action mailed October 24, 2001, and repeated in the Office Action mailed April 10, 2002, the Examiner stated that the odorants are not well understood nor adequately delineated making the claims ambiguous and unclear.

The Examiner merely restated his reasoning under Section 112, paragraph one (enablement), contending that the claimed odorants are highly subjective with respect to the

actual odors being encompassed due to variations in recipes of pumpkin pie or banana nut bread, variations in baby powder manufacturers, variations in cucumber brands, species, age/ripeness and geographic locations, a "distinct odor" of Good and Plenty™ from other licorice based products, and a "distinct odor" of milk chocolate compared to dark chocolate.

The Examiner also restated his reasoning that the odorants instantly disclosed and claimed have unusual functional effects, and thus should be limited to the disclosed commercial sources.

1. THE EXAMINER HAS APPLIED AN OVERBROAD INTERPRETATION TO THE LANGUAGE OF THE CLAIMS.

The Examiner has adopted a claim interpretation that ignores the way the terms are used in the art and in the specification.

The standard for interpreting claims during patent prosecution is well-established. Specifically, the standard guiding the USPTO when interpreting claims in an application is:

> [T]he PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definition or otherwise that may be afforded by the written description contained in the applicant's specification. *In re Morris*, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997).

The claims employ well-known language conventionally used in the art to which the invention pertains and this adequately defines the metes and bounds of the claimed invention, and which is of the same scope as the description of the invention contained in the disclosure. *In re Kamal*, 398 F.2d 867, 870, 158 USPQ 320, 322 (CCPA 1968).

The PTO's interpretation of claim terms should not be so broad that it conflicts with other patents from analogous art. The interpretation that one skilled in the art would give to a disputed term can be demonstrated by the use of the term in other patent references. *In re Cortwright*, 49 USPQ2d 1464 (Fed. Cir. 1999). Indeed, the PTO should not interpret claim terms to have meanings that "conflicts with the meaning given to identical terms in other patents from analogous art." *Id.*

Appellant believes the Examiner's interpretation of the terms "licorice-based odorant," "banana nut bread odorant," "cucumber odorant," "lavender odorant," "pumpkin pie odorant,"

"baby powder odorant," and "chocolate odorant," ignores the understanding in the art and the meaning given to the terms in other patents, and fails to take into account the description provided in the specification to define those terms.

The specification qualifies the odorants as those that effectively alter blood flow to the vagina. As discussed above, this effect can be readily ascertained by routine screening according to Appellant's provided description and the working example.

The Examiner should reconsider and withdraw his interpretation of the claim language and construe the terms in the claims as those terms are used in the art and understood according to the specification.

2. THE ART STRONGLY SUPPORTS APPELLANT'S INTERPRETATION OF THE TERMS.

Appellant submits the following documents as evidence of how one skilled in the art uses and understands the terms "licorice-based odorant," "cucumber odorant," "lavender odorant," "pumpkin pie odorant," "baby powder odorant," and "chocolate odorant," and to show the acceptance of these terms in the art, as well as the use and construction applied to these terms by the USPTO. For example, three U.S. patents issued to Appellant Hirsch and U.S. Patent 4,463,016 to Burgess use these terms and are in the same U.S. class (424) as the patent application under consideration.

Importantly, U.S. Patent 5,885,614 (Hirsch) (Use of odorants to treat male impotence, and article of manufacture therefor) describes a situation similar to the present application where odorants are used and claimed in a *method and article of manufacture for increasing penile blood flow in a male individual*. Commercial sources for the odorants are provided in the specification at col. 2, lines 40-43. Several of the presently claimed odorants are recited in the claims, for example, Claims 1, 2 and 4 below (emphasis added):

> 1. A method of *increasing penile blood flow* in a male individual, comprising:
> administering to the male by inhalation of an odorant in an amount effective to increase penile blood flow; the odorant selected from the group consisting of orange, a mixture of *lavender* and *pumpkin pie* a mixture of doughnut and *black licorice*, a mixture of *pumpkin pie* and doughnut lily of the valley, *black licorice*, a mixture of doughnut and cola, a mixture of *black licorice* and cola, a mixture of *lavender* and doughnut, *chocolate*, strawberry, rose, green, apple, parsley, peppermint, musk, *lavender*, vanilla, cranberry, pink grapefruit, floral,

baby powder, oriental spice, cinnamon buns, roasting meat, cheese pizza, doughnut, cola, *pumpkin pie*, and buttered popcorn.

2. A method of increasing penile blood flow in a male individual, comprising:
administering to the male by inhalation of an odorant in an amount effective to increase penile blood flow; the odorant selected from the group consisting of a mixture of *lavender* and *pumpkin pie*, a mixture of doughnut and *black licorice*, and a mixture of *pumpkin pie* and doughnut.

4. An article of manufacture, comprising:
(a) an odorant as recited in claim 1 packaged within a container, wherein the odorant when inhaled by a male individual is effective to increase penile blood flow; and
(b) instructions for use of the odorant according to the method of claim 1.

U.S. Patent 5,759,521 (Hirsch) (Method of altering perception of relative space of an area) identifies a cucumber odorant as useful (col. 1, line 66 to col. 2, lines 3 and lines 31-34:

> "...a substance having the characteristics of a green apple odorant, *cucumber odorant*, or seashore odorant is administered to a patient to cause the patient's perception of a confined area to become altered and expanded..."

and commercial sources of the odorants (at col. 2, lines 45-47).

U.S. Patent 6,106,837 (Hirsch) (Method of treating headaches, and article of manufacture therefor) identifies lavender odorant as useful and provides several commercial sources of the odorants (at col. 3, lines 31-37):

> An example of such an odorant is a substance having the characteristic of a green apple odor such as isoamyl isovalerate. Other useful odorants include, for example, banana, peppermint, and *lavender*. Such odorants are available commercially, for example, from International Flavors and Fragrances, Inc. (IFF, New York, N.Y.), Energy Essentials, Aroma Tech, and as essential oils.

U.S. Patent 4,463,016 (Burgess) (Method for the treatment of razor bumps) describes a topical composition that can include a "fragrance such as *cucumber fragrance* No. 24." See col. 2, line 59. The odorant is also recited in Claim 6 below (emphasis added):

> 1. A method for the treatment of razor bumps which comprises topically administering to an individual suffering from razor bumps an effective amount of a compound of the Formula: [formula] wherein R_1 and R_2 are C_1–C_7 alkyl in combination with a vehicle which facilitates topical application of the compound of Formula I.
>
> 6. The method according to claim 5 wherein said vehicle is composed of ingredients selected from the group consisting of propylene glycol, purified water, lanolin, sodium stearate, polyethylene glycol monostearate, sesame oil, cetyl alcohol, methyl paraben, propyl paraben, camphor and *cucumber fragrance.*

Also importantly, the Doty publication (Philadelphia Sensorics, 1983) — cited by the Examiner —lists *licorice, chocolate,* and *pumpkin pie odorants*, among others (Doty at page 7).

Such use clearly shows that one skilled in the art uses and understands the terms "licorice-based odorant," "banana nut bread odorant," "cucumber odorant," "lavender odorant," "pumpkin pie odorant," "baby powder odorant," and "chocolate odorant." Equally important, the above patents, particularly USP 5,885,614 issued by the USPTO with claims to a method and article of manufacture to increase penile blood flow, demonstrate that the presently used odorant terms are accepted and well understood in the art and by the USPTO. As such, the Examiner's interpretation of the claims is overbroad in view of how the term is used and understood by one skilled in the art and conflicts with the meaning give to identical terms in other patents from analogous art.

3. THE EXAMINER HAS FAILED TO TAKE INTO ACCOUNT THE WRITTEN DESCRIPTION AND THE LIMITATIONS IN THE CLAIMS WHEN INTERPRETING THE MEANING OF THE TERMS OF THE CLAIMS.

The specification clearly states that the odorants and odorant mixtures are capable of altering blood flow to the vagina when inhaled by a female individual, and this feature is recited in the claims.

The nature of the recited odorants is well understood in the odorant arts, and one skilled in the odorant arts would readily identify suitable odorants from various sources – both synthetic and natural – that have the recited odorant character and would achieve the desired effect. As recited in the claims, suitable odorant mixtures are those having the recited characteristic of a mixture of: a) a licorice-based odorant and banana nut bread odorant, b) a licorice-based odorant and a cucumber odorant, c) a lavender odorant and a pumpkin pie odorant, and d) a baby powder odorant and a chocolate odorant, which are capable of altering blood flow to the vagina when inhaled by a female individual.

The above arguments demonstrate that the inventor clearly uses the terms "licorice-based odorant," "banana nut bread odorant," "cucumber odorant," "lavender odorant," "pumpkin pie

odorant," "baby powder odorant," and "chocolate odorant" as such terms are commonly used in the art. The Examiner improperly interprets the claim limitations as being overbroad.

Based on Appellant's disclosure and the understanding in the art, the Examiner's finding that the claims are indefinite is in error. One of ordinary skill in the art would readily identify and use both synthetic and natural sources of the recited odorants other than the commercial sources of odorants disclosed in the specification, to provide the claimed articles of manufacture.

As such, Appellant believes that the claims are clear in their meaning and that the language of the claims is definite and correct, and requests that the Examiner withdraw the rejection.

IX. REQUEST

For the reasons stated in the above argument, Appellant believes that the claims on appeal comply with 35 U.S.C. § 112, and requests that the final rejection of the claims on appeal be reversed.

Respectfully submitted,

Kristine M. Strodthoff

Dated: September 3, 2002

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APPENDIX

WHAT IS CLAIMED:

24. An article of manufacture, comprising, packaged together:

a unit dosage amount of an odorant packaged in a container, to alter blood flow to the vagina when inhaled by a female individual; wherein the odorant is selected from the group consisting a mixture of licorice-based and banana nut bread odorants, a mixture of licorice-based and cucumber odorants, a mixture of lavender and pumpkin pie odorants, and a mixture of baby powder and chocolate odorants; and

instructions for administering the odorant to alter blood flow to the vagina.

25. An article of manufacture, comprising, packaged together:

a unit dosage amount of an odorant packaged in a container, to alter blood flow to the vagina when inhaled by a female individual;

instructions for administering the odorant to alter blood flow to the vagina; and

at least one of the following:

a device for measuring blood flow to the vagina of the female individual; and

means for testing olfactory ability in the female individual.

26. The article of manufacture of Claim 24, wherein the unit dosage amount comprises a concentration of the odorant effective to provide a suprathreshold but not irritant amount of the odorant.

27. The article of manufacture of Claim 24, wherein the unit dosage amount comprises a concentration of the odorant at about 25-55 decismel units.

28. The article of manufacture of Claim 24, wherein the odorant is packaged within a delivery device selected from the group consisting of a vial, jar, pouch, can, bottle, blister pack, and a scratch-and-sniff odor patch containing microcapsules of the odorant.

29. The article of manufacture of Claim 24, wherein the odorant is in a form selected from the group consisting of a cloth scented with the odorant, an aerosol spray, a pump-type spray, a nasal spray, a liquid or solid form of the odorant contained in a vessel having a cap, a liquid or solid form of the odorant contained in a blister pack, and microcapsules of the odorant contained in a scratch-and-sniff odor patch.

30. The article of manufacture of Claim 24, wherein the odorant is in the form of a cream or a cologne.

31. The article of manufacture of Claim 24, wherein the odorant is in a liquid form contained in a dispenser.

32. The article of manufacture of Claim 31, wherein the dispenser comprises a capped vessel having a tip impregnated with the odorant.

33. The article of manufacture of Claim 32, wherein the dispenser contains the odorant absorbed to a wicking material.

35. An article of manufacture, comprising, packaged together:

a unit dosage amount of an odorant packaged in a container, to alter blood flow to the vagina when inhaled by a female individual; wherein the odorant comprises a mixture of a licorice-based odorant and a cucumber odorant; and

instructions for administering the odorant to alter blood flow to the vagina.

36. The article of manufacture of Claim 24, wherein the odorant and the unit dosage amount of the odorant is effective to increase blood flow to the vagina of the female individual by about 10-30%.

38. The article of manufacture of Claim 24, wherein the odorant and the unit dosage amount of the odorant is effective to decrease blood flow to the vagina of the female individual by about 10-20%.

41. An article of manufacture, comprising, packaged together:

a unit dosage amount of an odorant packaged in a container, to increase blood flow to the vagina when inhaled by a female individual; wherein the odorant is selected from the group consisting of a mixture of a licorice-based and cucumber odorants, a mixture of a lavender and pumpkin pie odorants, and a mixture of a baby powder and chocolate odorants; and

instructions for administering the odorant to increase blood flow to the vagina.

42. The article of manufacture of Claim 41, wherein the odorant and the unit dosage amount of the odorant is effective to increase blood flow to the vagina of the female individual by about 10-30%.

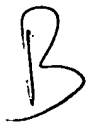
44. The article of manufacture of Claim 41, wherein the odorant comprises a mixture of a licorice-based and cucumber odorants.

45. An article of manufacture, comprising, packaged together:

a unit dosage amount of an odorant packaged in a container, to decrease blood flow to the vagina when inhaled by a female individual; wherein the odorant is a mixture of licorice-based and cucumber odorants; and

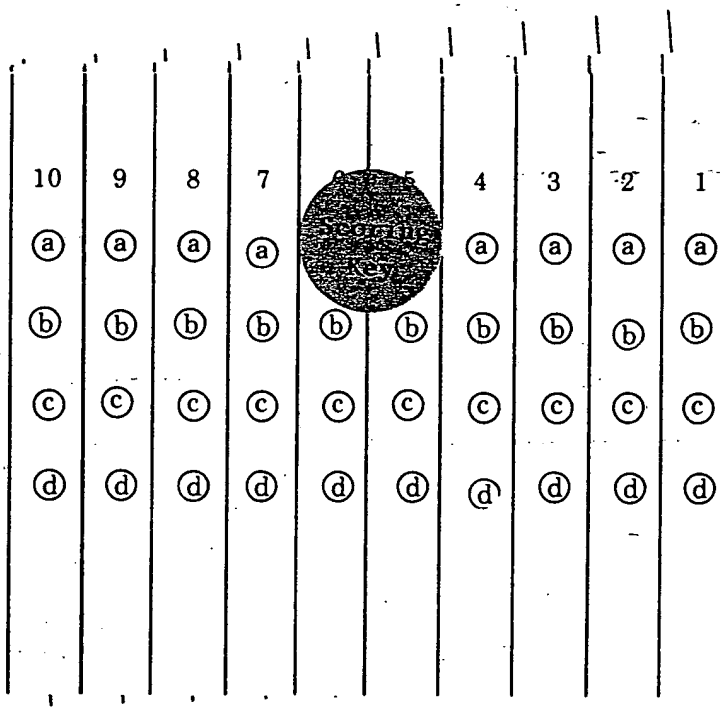
instructions for administering the odorant to decrease blood flow to the vagina.

46. The article of manufacture of Claim 45, wherein the odorant and the unit dosage amount of the odorant is effective to decrease blood flow to the vagina of the female individual by about 10-20%.



DOTY

THE SMELL IDENTIFICATION TEST™
ADMINISTRATION MANUAL



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THE SMELL IDENTIFICATION TEST™ ADMINISTRATION MANUAL

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GENERAL INTRODUCTION

The purpose of this manual is twofold -- first, to provide information and normative data for valid administration and scoring of the Smell Identification Test™ (even by personnel not specifically trained in psychometric or sensory testing) and second, to review the initial studies of its development and application. Because this measuring instrument has only been recently developed, many of its potential uses have not been explored and even its most obvious applications have yet to be made. For this reason, this manual will be up-dated from time to time to include the results of more recent studies. Sensonics, Inc. would appreciate being informed of results and publications based upon the application of this test so that this information can be made available in subsequent editions of the manual.

Until the development of the Smell Identification Test™, no convenient means for quantitatively assessing smell function in a standardized manner was generally available. By incorporating microencapsulation technology and sound psychometric principles, the Smell Identification Test™ clearly filled this void. Despite the fact that the test was initially envisioned to provide only a first-step olfactory "screening" function, it became quite clear in both the clinic and laboratory that the test was much more broadly useful than initially anticipated. Indeed, it was found to be sensitive to a number of subject variables and to correlate more closely, in the clinical setting, with patients' complaints and other indices of dysfunction than measures from more traditional threshold and suprathreshold psychophysical tests. Furthermore, its high reliability has allowed it to be used in situations where previous odor identification tests were found wanting.

There is no doubt that this test has limitations in some subject groups and in some test situations, and future work will better define the limits of its applicability. For example, the test cannot be validly administered to persons with limited language ability. However, as indicated by the normative data contained in a subsequent section of the manual, it is applicable to nearly all English-speaking individuals beginning at a very young age. The test is currently being translated into several other languages and the interested investigator should contact Sensonics, Inc. for details of the release of these versions of the test. In addition, a non-verbal version of the test will soon be available for use in testing very young persons or individuals with limited language ability.

Overall, the available research data suggest the Smell Identification Test™ is highly sensitive, broadly applicable, and very useful in situations where dysfunction of the olfactory sense is present or suspected. In addition, such data indicate that it is helpful in discriminating between persons with mediocre smell function and those with a more highly developed sense of smell, as is needed in the screening of sensory panels for various industrial applications.

This manual is organized into two major sections. The first section is a review of the research work that went into the development of the test, whereas the second is a presentation of the procedures that should be followed for its valid administration.

It is absolutely essential that the test administrator be familiar with Section II, as it provides details of how the test should be administered and scored.

Although it is not absolutely necessary to read Section I of the manual to validly use the test, it is recommended that this material be read by the test administrator. A knowledge of this information will provide a better understanding of the strengths and weaknesses of the instrument which, hopefully, will translate into its most appropriate application and interpretation.

SECTION I

Development of the Smell Identification Test™

Although the initial studies describing the development of the Smell Identification Test™ are presented elsewhere [1-3], a brief overview of their procedures and findings is presented in this section. For the sake of brevity and clarity, many of the methodological and statistical details are omitted, and the interested reader is referred to the earlier publications for more specific information.

Five initial experiments, outlined in order below, led to the development of the Smell Identification Test™, although the test had as its basis an earlier prototype mentioned elsewhere [4]. In the first two experiments of this series [see 3], selection of the most appropriate stimuli was made. Subsequently, the influences of variables such as the age, gender, and ethnic background of the subjects on the scores of the developed test were examined. In the third experiment, the utility of the test in discriminating among persons with known or suspected olfactory disorders, as well as persons instructed to feign total anosmia, was established. In the fourth experiment, the instrument's test-retest reliability was determined, whereas in the fifth its scores were compared to measures derived from a traditional detection threshold procedure.

Experiment 1

Experiment 1 had four main goals. The first was to quantitatively establish, in subjects with no apparent olfactory dysfunction, psychological ratings of the perceived intensity, pleasantness, familiarity, coolness-warmth, and irritation of 50 Microfragrance samples™ of potential use in a standardized olfactory test. Such data provided basic information as to the suitability of microencapsulated odorants for testing human olfaction, as well as a basis for eliminating stimuli with problems of identifiability, irritability, or intensity from the final version of the test. The second goal was to determine whether such ratings were influenced by two means of releasing the odors from the microencapsulated crystals (scratching the surface with #120 sandpaper or with a pencil tip) and, if so, whether one means was clearly preferable to the other. The third goal was to ascertain if males and females differentially rated the stimuli (as was expected if odorants released from microencapsulated crystals behaved similarly to those from other stimulus sources; see 5-7), whereas the fourth goal was to

ascertain the relative identifiability of the 50 Microfragrance samples™ when no verbal or written cues were provided as to their identity. This information, in conjunction with that collected in the next study (Experiment 2), was utilized to eliminate stimuli that were difficult to identify.

Fifty men and women (half of each sex; mean age = 24.87 yrs, SD = 5.52 yrs) with self-reported normal smell function rated the intensity, pleasantness, coolness/warmth, irritation, and familiarity of 50 microencapsulated odorants on standard 9-point category rating scales [see 8]. The stimuli were chosen on the basis of a number of criteria, including (a) being composed of single, as well as of multiple, components (given the possiblity that the olfactory system codes information using a multiple profile/multiple receptor site process; 9), (b) spanning a number of qualitative odor classes [10], (c) evidencing (in most cases) no intranasal trigeminal stimulative properties, and (d) evidencing, in selected cases, clear-cut trigeminal stimulative ability to allow for possible detection of malingering [8].

In general, the results indicated that (a) none of the 50 odorants were perceived too extreme on any of the continua to warrent immediate exclusion from further consideration as test stimuli (Figure 1), (b) the odors differed among one another on each of the perceived attributes (Figure 1), (c) women rated the odors, on the average, as slightly more intense, more unpleasant, less cool, less irritating, and more familiar than did men, and (d) that both the sandpaper and pencil release procedures produced reasonably similar results (Figure 1). However, a few slight differences were observed between these two modes of releasing the stimuli. For example, the stimuli were rated, on the average, as slightly more familiar and less pleasant when released by sandpaper than when released by pencil. In addition, women rated stimuli released by pencil as slightly stronger (although of equal familiarity) than those released by sandpaper. Despite the fact that there was a significant tendency for the familiarity ratings to differ between the sexes as a function of the odorants evaluated, the stimuli rated as more familiar by men than by women did not differ in any obvious way from the other odorants.

Based on the findings that odors released by pencil were judged slightly less familiar than those released by sandpaper, and that women rated odors released by sandpaper stronger than odors released in this manner by men [in accord with the sex difference noted in other human olfactory work (e.g., 5-7)], sandpaper was chosen as the means for releasing the stimuli in subsequent studies.

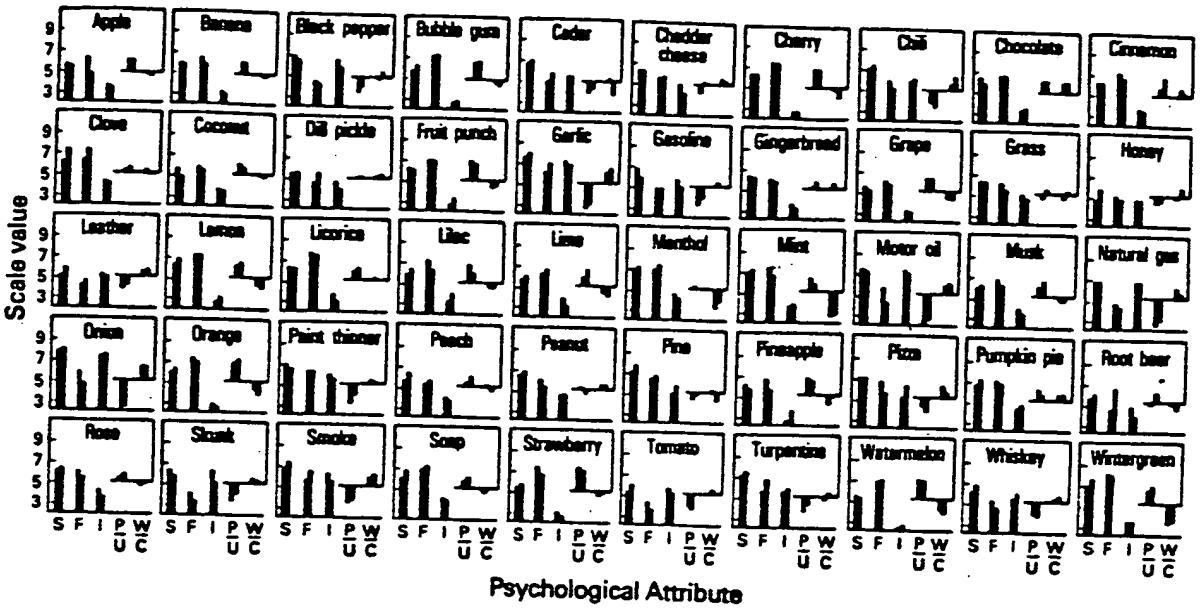


Fig. 1: Mean category ratings given to 50 microencapsulated odorant strips using #120 sandpaper (left half of each vertical bar) or the tip of a #2 lead pencil (right half of each vertical bar). S = Strength (intensity); F = Familiarity; I = Irritation; P/U = Pleasantness/Unpleasantness; W/C = Warm/Cool. For the P/U and W/C scales, the horizontal line signifies the neutral reference point. Note, for example, the marked unpleasantness and irritation ratings given to onion, but not to rose, and the coolness attributed to menthol. From [3] with permission.

Experiment 2

Experiment 2 had three main goals: First, to determine the relative identifiability of the stimulants in a forced-choice situation where alternative responses were provided; second, to omit stimuli from inclusion in the test which were not correctly identified by the majority of a large number of normal subjects; and third, to evaluate the relative influences of several subject variables, alone and in combination, upon the test scores of a large and heterogeneous group of subjects.

In the initial phase of the study (where the identifiability of the odorants was established), 1198 subjects were tested. These volunteers consisted of (a) participants of regional health fairs and public events, (b) primary and secondary public school students, (c) university students, (d) residents of homes for the elderly, and (e) employees of the Hospital of the University of Pennsylvania. Persons reporting any smell abnormalities or who were unable to correctly identify at least half of the stimulants were not included in this study group. Seventy-three percent

were White Americans and 21% Black Americans, with most of the remaining 6% not indicating their ethnicity. Sixty-two percent were female and 38% male. Eighty percent were current non-smokers, and 19% current smokers, with the remainder not reporting this information. Although a wide spectrum of ages was present in this group, disproportionately more subjects fell within the younger age ranges, as indicated by the following statistics: mean age = 35.24 (SD = 19.21); modal age = 19.0; median age = 29.29; 25th percentile = 18.88; 75 percentile = 50.3. Overall, the average ages of the two sexes, of the two major ethnic groups, and of the smokers and non-smokers were similar [see 31].

In the second phase of this study (where the influences of age, gender, race, and smoking habits upon the test scores were evaluated by multiple regression analysis), the data from most of the subjects mentioned above and from an additional number of persons (mostly elderly) were subjected to analysis. Although test scores of 1365 subjects were initially evaluated, data from 26 with apparent anosmia were omitted from the data set upon which the final regression equation was computed.

A preliminary 50-item 5-booklet Smell Identification Test™ was developed for administation in Experiment 2. In this test, which was identical in general format to the 40-item version, the 50 stimulants were presented in random order, with the exception that odors of similar psychological quality (e.g., garlic and onion) did not directly follow one another.

To aid in the selection of sets of distinct discriptors for the multiple alternative choices of each of the 50 items, the names of 51 descriptors were typed on small cards. Fifty of these names were those assigned by the manufacturer to the Microfragance samples™*, whereas one was that of "cola". These cards were then arranged by two female technicians and the author spatially on a table top with the goal of making the distances between the cards proportional to the psychological stimilarity of the odor items. For example, the garlic and onion written labels were located close to one another, whereas the chocolate and gasoline labels were placed apart from one another and at differing distances from those of onion and garlic. This simple procedure resulted in a two-dimensional space from which the three "distractor" items were selected for each odorant so as to insure their distinctiveness from one another as well as from the odorant of interest.

*Microfragrance samples™ is a registered trademark of the 3M Corporation, St. Paul, Minnesota.

In addition to sampling response alternatives relatively distinct from one another, an attempt was made to to use each of the verbal descriptors equally often and about the same number of times in the four response category positions (a,b,c & d). Although it was not possible to achieve all of these aims simultaneously, this goal was approached. Thus, 37 of the 51 descriptors appeared four times apiece, eight three times apiece, five five times apiece, one six times, and another once. No descriptor ever appeared more than twice in any of the response category positions.

As indicated in Figure 2, it was apparent that a number of the Microfragrance samples™ were poorly identified by the majority of the subjects, even though the responses were cued by written alternatives. Based on these findings and other identifiability

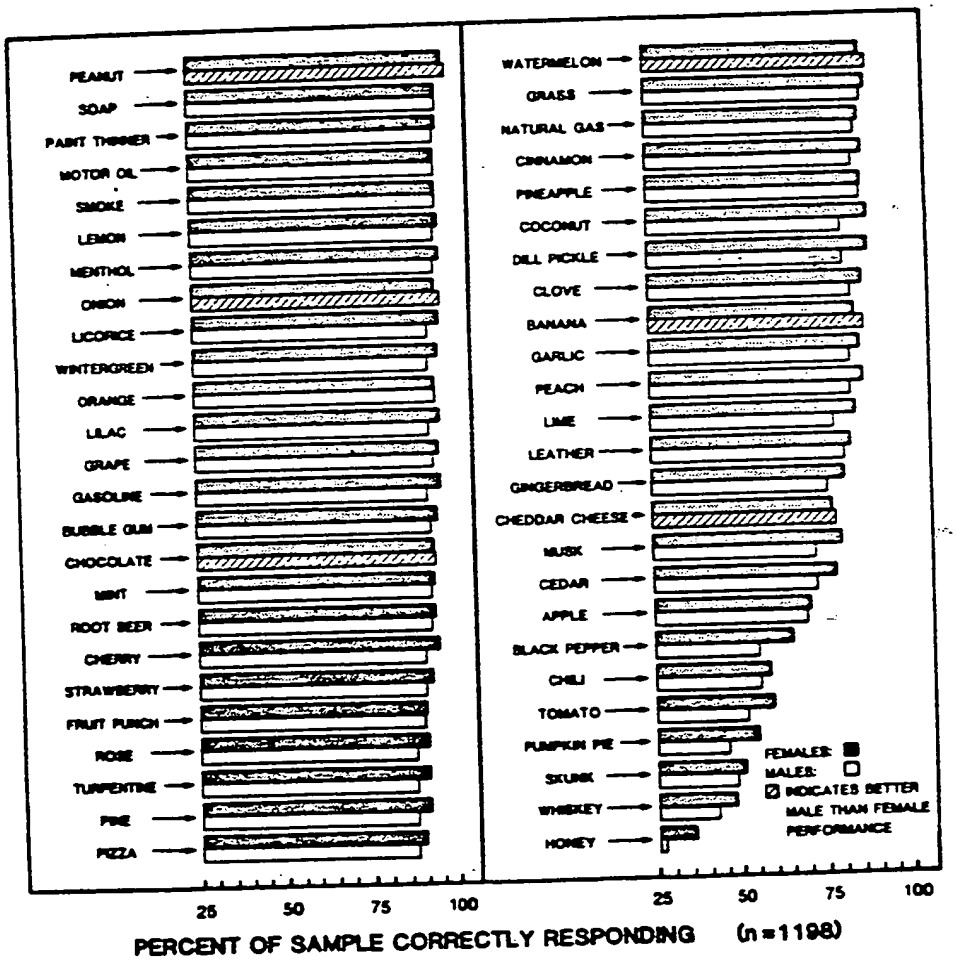


Fig. 2: Percent of subjects correctly identifying each of the 50 target microencapsulated odorants presented in a 4-alternative forced-choice response paradigm. Note that women performed better than men on most of the stimuli. From [3] with permission.

data published elsewhere [3], the following stimuli were eliminated from inclusion in the 40-item final version of the Smell Identification Test™: apple, black pepper, chili, honey, musk, pumpkin pie, skunk, tomato, and whiskey. In addition, garlic was eliminated from the final test due to its psychological similarity to onion.

To determine what influence a number of demographic variables had on the test scores (for the 40 items included in the final test), a series of multiple regression analyses were performed on data from 1339 to 1365 subjects (missing data for some variables necessitated using fewer subjects in some instances). The final regression equation fitted to subjects with Smell Identification Test™ scores 20 or greater included only variables significant at the .05 level (n = 1339):

$$Y = 33.399 + 1.055X_1 + 0.217X_2 - 0.003X_2^2 - 0.489X_3 - 1.008X_4 - 1.040X_5 - 2.172X_6 + e,$$

where X_1 = 1 (0) if the subject is female (male); X_2 = age of subject in years; X_3 = 1 (0) if the subject does (does not) currently smoke; X_4 = 1 (0) if the subject is (is not) nonwhite; X_5 = 1 (0) if the subject does (does not) report a smell problem; X_6 = 1 (0) if the subject does (does not) belong to an elderly sub-file (i.e., persons primarily in old-age homes who are over 65 yrs of age), and e = error term.

The R^2 value of this equation was 0.411 (SD = 3.318), and the standard errors of estimate for the seven variables were as follows: X_1 = .188; X_2 = .023; X_2^2 = .0003; X_3 = .238; X_4 = .222; X_5 = .302; and X_6 = .525.

Overall, these analyses indicated that gender, age, ethnic background, and smoking habits all relate significantly to scores on the Smell Identification Test™. Obviously, gender and age account for most of the variance. The relation between age, gender and Smell Identification Test™ scores is depicted in Figure 3. Note that men evidenced lower average test scores than women within nearly all age groups, and that both sexes evidenced a decrease in test performance beginning in the sixth decade of life which continued through the ninth decade.

To establish if the decrease in the scores across the older ages was due, in whole or in part, to a general decrement in memory function, the Wechsler Memory Scale (WMS, Form II) [11] was administered to 47 persons above 55 yrs of age within a day of the olfactory tests (mean age = 81.32, SD = 7.75). Because 16 of

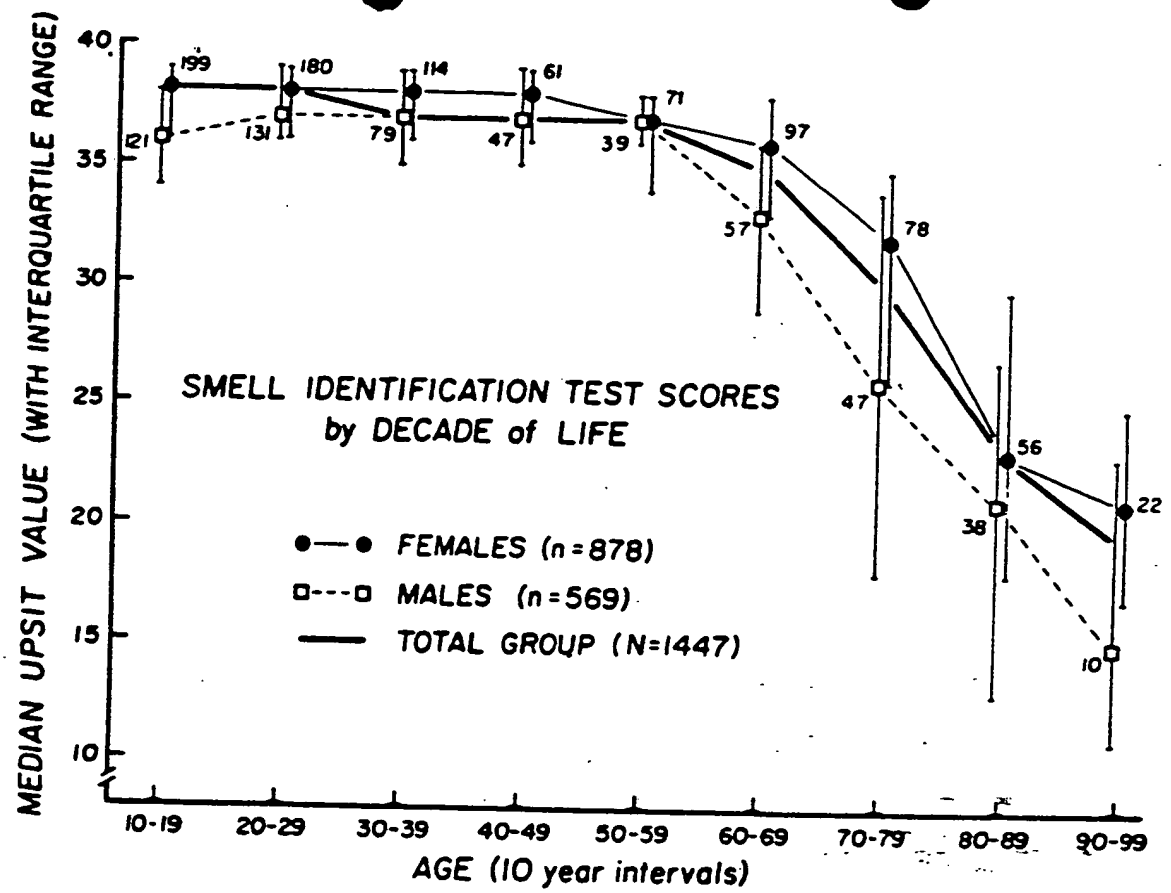


Fig. 3: Relationship between Smell Identification Test™ scores, age, and gender in a large heterogeneous group of subjects. From [3] with permission.

these individuals evidenced total anosmia, only data from those scoring 20 or above were subjected to analysis. As indicated in detail elsewhere [3], partial correlations revealed that no appreciable relationship was present between the Smell Identification Test™ scores and the WMS scores (r = .027, ns), despite the fact that both of these tests significantly correlated with age, per se [r (smell score, age) = -.51, $p <$ average Smell Identification Test™ scores with age reflects a perceptual deficit largely independent of the memory deficit measured by the Wechsler Memory Scale.

Experiment 3

The goal of Experiment 3 was to validate the Smell Identification Test™ by establishing its ability to distinguish among (a) persons with normal olfactory function, (b) persons with known or suspected olfactory dysfunction, and (c) persons instructed to feign total anosmia under the make-believe condition of receiving a large insurance payment if they successfully did so.

Five groups of subjects were administered the test:

(a) 1215 persons with normal smell function (mean age = 33.69 yrs, SD = 17.69; essentially the study population evaluated in Experiment 2 minus persons over the age of 65);

(b) 51 persons with total bilateral anosmia (mean age = 40.76 yrs, SD = 20.75); 15 had Kallmann's syndrome, with the remainder being anosmic from a number of causes [see 3]);

(c) 21 men with Korsakoff's syndrome (mean age = 57.05, SD = 8.13), an organic brain syndrome associated with a consistent pattern of lesions in the midline areas of the brainstem and diencephalon and impairment on numerous tests of olfactory function [15-17];

(d) 31 persons with multiple sclerosis (mean age = 49.03, SD = 12.56); and

(e) 158 persons with normal smell ability who were instructed to feign total anosmia under the make-believe condition that they would collect a large sum of money from an insurance company if they successfully did so. One hundred and three of these individuals had a least one year of college, whereas the remainder had a high school education or less.

As indicated in Figure 4, persons with total bilateral anosmia evidenced scores on the Smell Identification Test™ only slightly above the number expected on the basis of random responding (Mean number correct = 12.25, SD = 3.04; Median = 13). This slightly higher than chance performance was due to the inclusion of several trigeminal stimulants in the test.

Most of the Korsakoff patients evidenced aberrant scores, with a wide range in the degree of deficit being present (Mean = 15.95, SD = 7.97; Median = 14; Range = 5 - 37; Figure 4). The recent demonstration of a high correlation between scores on the Smell Identification Test™ and lumbar CSF levels of 4-methoxy-3-hydroxy-phenyl glycol (a major metabolite of norepinephrine) in a subgroup of these patients suggests that the divergent scores may reflect the degree of CNS noradrenergic pathway damage [12]. Assuming this to be the case, the Smell Identification Test™ may serve, at least in these types of patients, as a nonobtrusive index of the degree of such CNS damage.

Patients with multiple sclerosis typically scored within the normal range, although a disproportionate number fell into the

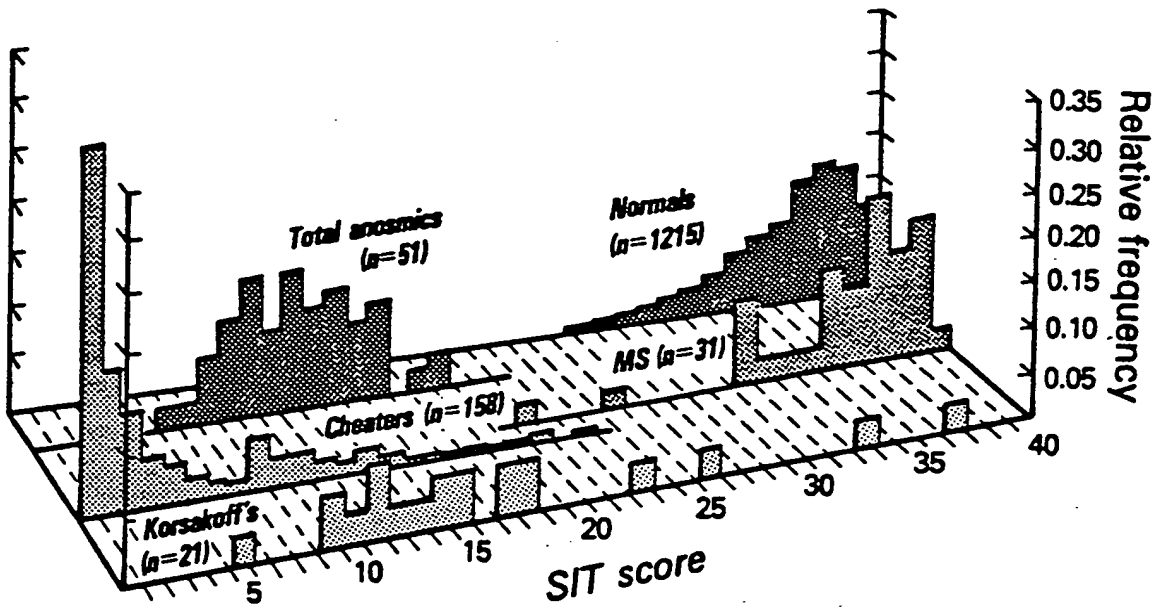


Fig. 4: Smell Identificaton Test™ scores for five groups of subjects. SIT = Smell Identification Test. See text for details. From [3] with permission.

lower section of this range, and two fell outside this range (Figure 4). A partial correlation (factoring out the effects of age, per se) revealed a weak but statistically significant relationship between the Smell Identification Test™ scores and the estimated duration of the disease ($r = -.428$, $p < .05$).

It is apparent in Figure 4 that subjects asked to feign total anosmia reported fewer correct responses than expected on the basis of random responding or than observed in persons with well-documented total anosmia. Indeed, the modal number correct in this group was zero. Overlap between the distribution of these "cheaters" with that of the total anosmics was minimal. No differences were observed between the responses of the college-educated and non-college educated subjects.

Experiment 4

A major factor which determines the usefulness and validity of a test is its reliability or stability over time; i.e., its ability to consistently measure what it is intended to measure. The purpose of Experiment 4 was to determine the test-retest reliability of the Smell Identification Test™.

Twenty-three women and 30 men (mean age = 44.1 yrs, SD = 19.98) were selected from our subject population for readministration of the Smell Identification Test™ at an interval exceeding six months from the time of the initial test. To allow for a valid computation of the test-retest reliability coefficient, we selected persons who represented the entire continuum of possible scores on the initial test. The final study group consisted of five persons with initial test scores in the 6 to 11 range, seven with scores in the 11 to 15 range, four with scores in the 16 to 20 range, thirteen with scores in the 21 to 25 range, five with scores in the 25 to 30 range, eight with scores in the 31 to 35 range, and eleven with scores in the 36 to 40 range.

As indicated in Figure 5, the scores were extremely stable despite the long interval between the two test administrations. The Pearson r between the two sets of test scores was .918 ($p <$ regression line fitted to these data (1.409) suggests the possibility that at least some of the subjects improved their performance slightly on the second test administration. Whether this slight change reflects a change in olfactory function or simply is due to sampling artifacts requires further study.

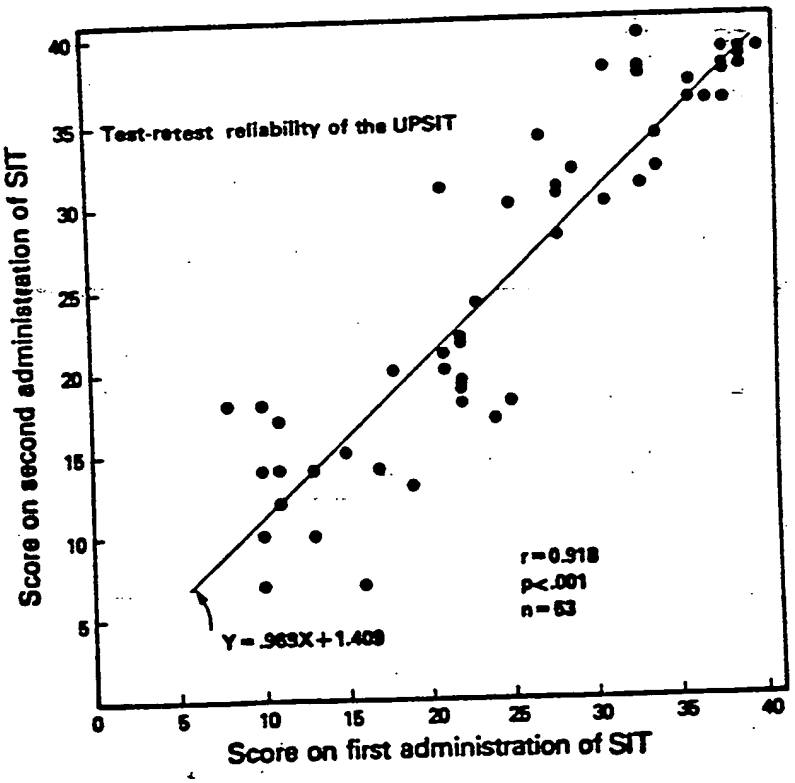


Fig. 5: Test-retest relation between Smell Identification Test™ scores in a group of subjects tested on two occassions separated by a minimum of six months. From [3] with permission.

Experiment 5

The goal of Experiment 5 was to ascertain whether scores on the Smell Identification Test™ correlate significantly with measures from a traditional odor detection threshold task. Although, theoretically, scores on a suprathreshold identification task need not correlate with detection threshold values, some degree of relationship would be expected if both tests were sampling a common domain of olfactory function.

Sixty-four men and women (mean age = 42.41; SD = 18.93) were evaluated. With the exception of six college students, these individuals were patients at the Smell and Taste Center of the Hospital of the University of Pennsylvania and evidenced varying degrees of olfactory function. Thus, a comparatively broad range of scores on both the Smell Identification Test™ and the threshold test was represented.

The subjects were administered the two tests on the same day. The threshold test was a slight modification of the forced-choice single-staircase procedure described by Ghorbanian et al [21]. A trial consisted of the presentation of two 100 ml glass sniff bottles in rapid succession in a standardized manner [see 8]. One bottle contained a given concentration of perfume-grade phenyl ethyl alcohol (a rose-like odorant relatively free of trigeminal stimulative ability) dissolved in 20 ml of propylene glycol, whereas the other contained 20 ml of propylene glycol alone. The subject indicated which of the two randomly-presented bottles evoked the stronger sensation. Even if no difference was noted, the subject was required to choose one or the other bottle. No feedback was provided as to the correctness of the responses.

The staircase was begun around the -6.0 log concentration step of a half-log step (volume/volume) dilution series extending from -6.50 to -1.00 log steps (two trials per step) and moved upwards in single log steps until correct detection occurred on two successive trials. At this point, two additional trials at that concentration level were given to decrease the likelihood of chance performance at that concentration. If a correct response did not occur on both of these trials, the staircase was moved upwards in 1.00 log steps until detection occurred on four consecutive trials at a given concentration. When correct responses occurred on all four trials, the staircase was reversed and subsequently moved up or down in 0.50 log increments or decrements, depending upon the subject's performance. Thus, the staircase was moved up 0.50 log units if an incorrect response occurred on either of the two trials, and down 0.50 log

increments if a correct response occurred on both trials. If an incorrect response occurred on the first of the two trials, the second trial was not run and a new pair of trials was begun at the appropriate next higher concentration. A minimum of 20 seconds was interposed between the pairs of trials. The geometric mean of the first four staircase reversal points following the third staircase reversal was used as the threshold measure. In cases where a subject's threshold was located outside the -6.50 to -1.00 log concentration range, the procedure of assigning the subject either the -6.50 or the -1.00 log step value, as appropriate, was adopted.

The relation between the Smell Identification Test™ scores and the detection threshold values is presented in Figure 6. Although the correlation between the two sets of measures was remarkably strong ($r = -0.89$, $p < .001$), it was likely inflated by the large number of scores of total anosmics which clustered at the lower end of the continua. When these scores (see box in Figure 6) were omitted from the computation, the correlation coefficient was -0.794 [$p < .001$].

A discussion of the findings of Section I in relation to other literature studies is presented in another publication [3].

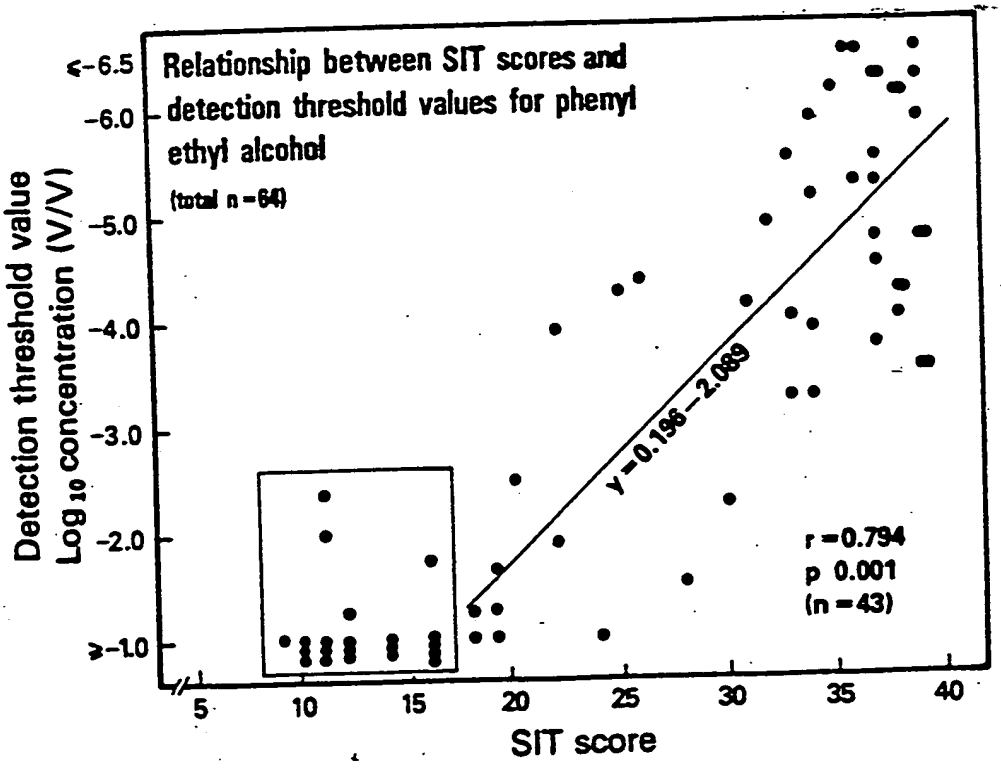


Fig. 6: Relationship between detection thresholds for phenyl ethyl alcohol and Smell Identification Test™ scores. From [3] with permission.

SECTION II

Administration and Scoring of Smell Identification Test™

Section II should be carefully read before administering the Smell Identification Test™. As with any psychometric instrument, the Smell Identification Test™ should be administered only by qualified professional personnel. Furthermore, the norms for this test and this manual should never, under any circumstances, be given to anyone not professional engaged in the scientific or medical evaluation of smell function. We recommend that this test manual and the copies of the Smell Identification Test™ be stored in a locked secure place when not in use and that, under no circumstances, the examinee be allowed to keep the test or be given direct access to its means of scoring. To insure the validity of the test, tests stored over 6 months should be evaluted by scratching the microencapsulated odor labels on a small corner section to be certain that the odors have not changed in quality.

Administration Procedures

The Smell Identification Test™ was designed to be self-administered by most literate individuals. However, care must be taken to insure that the instructions are followed exactly, and persons to whom the test is sent through the mail should be re-instructed (in a cover letter) as to the importance of providing a response to all items even if no odor is detected. In addition to failing to correctly follow instructions, some persons (particularly those with smell disorders) use the sandpaper too strongly when releasing the odorants and, essentially, sand the entire microencapsulated test strip down to the base paper. For this reason, it is best to inform the subject of this problem and to tell them to scratch the odorized surfaces by making only a few firm scrapes. For subjects being tested under supervision, it is best that the examiner or supervisor release the first odor for the subject by scratching the surface appropriately. The examiner should then indicate to the subject that this is the exact manner in which all subsequent odors should be released and that sanding is not permitted. It is essential that the subject read over the instructions before beginning the test, and that the items are sampled in chronological order. Immediately after completion of the test, the test administrator should examine it to insure that all items are complete. If not, the test should be returned to the subject immediately for completion of the

uncompleted items. Because the normative data are based upon all 40 items, incomplete booklets cannot be validly scored.

The examiner must help administer the test to persons who have impaired eyesight or who, on the basis of age or other factors, cannot read the alternatives or adequately release the odorants. In such cases, the examiner should obtain the information on the back of Booklet #1 verbally and fill it in for the subject and place the subject's name on the spaces provided on the other three booklets. The examiner should then use the sandpaper to correctly release the first odor, hold it under the subject's nose, and read aloud the response alternatives while the subject is sniffing the microencapsulated strip. In cases where the subject's eyesight is not impaired, it is permissible to allow the subject to read the alternatives as they are mentioned verbally. Finally, the examiner should mark the subject's response to each item on the columns provided on the booklet's response page. When extremely old people are tested with this instrument, it is permissible to spread the testing out over several sessions to minimize any problems associated with their attention spans or willingness to cooperate.

Because of the medical, psychological, and ethical considerations involved in assessing sensory function, it is imperative that the results of the Smell Identification Test™ be interpreted within the entire context of the individual's occupation, general health, and psychological state. For example, a score of 20 on the test is quite a different matter for a 40-year old chef than for a 40-year old sanitation worker. Likewise, as will be seen in the next section, the individual's age and gender must be taken into consideration when evaluating the test results. While a score of 20 is very abnormal for a 30 year old male (falling completely out of the range of a normal control group), such a score is not abnormal for an 80 year old male, where it would fall near the middle of the "normal" range. Assuming that the latter individual is healty, the information would be transmitted to him that while his smell ability is clearly diminished from what it was a few years before, it falls within the normal range of males within his age category.

Norms based upon the administration of the Smell Identification Test™ to 961 women and 649 men of various ages are presented in Tables 1 and 2. Despite these rather large sample sizes, it should be noted that these norms are currently being expanded and suffer from the limitation of having only a few subjects in certain age categories. For example, the numbers of children within the 4-5 yr age range is very small, necessitating caution in the interpretation of test scores from this group. The sample

of subjects upon which these norms was developed included most of the persons described in Experiment 2 of Section I of this manual. The remaining additional subjects largely consisted of more persons tested in homes for the elderly and children tested at various summer camps within the Philadelphia area. Although no claim can be made that these norms represent a truly random sample of the population at large, they represent the largest empirical collection of data on human smell function ever collected. Because of the large number of subjects examined, and because of the representation of persons from a wide range of education levels, occupations, ethnic backgrounds, and life styles, it is unlikely that these norms deviate markedly from the population as a whole. Future editions of this manual will include further breakdowns of population subgroups by factors such as occupation, ethnic background, etc., as sample sizes warrent. These norms will be updated from time to time as more "normal" individuals are evaluated.

Interpretation of a Subject's Test Score in Relation to Normative Data

The use of Tables 1 and 2 in determining an individual's percentile score is straightforward. First, the subject's total number of correct responses (maximum possible = 40) is established by use of the test's scoring key. Second, this test score is located in the far left column of Table 1 for women and Table 2 for men. The age group of the subject is then located along the top of the approprate table and the subject's percentile score is read as the intersection of the test score row and age group column. For example, if a 47 year old female scored 35 on the test, the percentile at which she falls would be the 15th. Thus, 15% of the group of "normal" females achieved a score at or below that value, with the remainder scoring above. Such a score is clearly at the lower end of the normal group, but not markedly abnormal, as would be a score of 10 for such an individual.

In general, the following criteria have been developed for establishing a patient's olfactory diagnosis using this test instrument. With the exception of boys aged 15 yrs or less and girls aged 10 yrs or less, this classification scheme is based upon a characterization of the test scores that is independent of the age of the subjects (e.g., despite the fact that a score of 18 is in the middle of the "normal" range of scores for a 77 year old male, it is still indicative of the absolute condition of anosmia). In this classification scheme, anosmia is defined as total inability to perceive qualitative odor sensations (independent of the "common chemical sense" sensations perceived

via the trigeminal nerve), whereas microsmia is defined operationally as decreased smell ability. The term microsmia was chosen to specifically relate to the scores on the Smell Identification Test™, and does not draw a distinction between "partial anosmia" and "hyposmia" [21]. Because the operational establishment of either of these latter conditions requires both the testing of a large number of odorants and a considerable amount of effort (both of which are not practical in the clinic), the term microsmia accurately describes the condition of lessened smell function without being operationally or conceptually related to concepts which cannot be objectively confirmed in the typical clinical situation. Even if time permitted extensive threshold testing in such a context, olfactory detection threshold measures are frequently misleading, as a number of totally anosmic individuals with inflammed intranasal membranes evidence normal or supranormal detection thresholds.

SMELL IDENTIFICATION TEST SCORE	OLFACTORY DIAGNOSIS
00 - 05	Probable Malingering
06 - 19	Total Anosmia
20 - 33	Microsmia (males only)
20 - 34	Microsmia (females only)
34 - 40	Normosmia (males only)
35 - 40	Normosmia (females only)

It should again be emphasized, as indicated in Tables 1 and 2, that these criteria do not apply in the case of boys aged 15 and below and girls aged 10 and below. For these individuals, the border between normosmia and microsmia has been adjusted downward to reflect the empirical distribution of their percentiles. It should also be emphasized that the choice of these cutoff values was made on empirical grounds. Thus, in the case of the total anosmia and probable malingering categories, results from totally anosmic individuals and persons instructed to malinger revealed these values to be the appropriate cutoffs (see Fig. 4 of this manual). In addition, detailed analyses of the substances that patients reported as being detectable revealed that patients with scores below 20 noted the detection of only household substances known to have strong trigeminal stimulative properties (unpublished data). The border between microsmia and normosmia was chosen to represent a value close to the 10th percentile of adults within the middle age range.

As more individuals are added to this data base, it is conceivable that these criteria may be modified slightly. At the present time, however, they serve as relatively well-defined points and generally allow accurate categorization of smell

Table 1: Percentile Table for Females (N = 961). Numbers in body of table are percentile scores corresponding to Smell Identification Test™ scores in each age category. Numbers at bottom of table refer to sample sizes within each age category. The three solid lines crossing the columns of percentile scores represent, from bottom to top, the regions of the 25th percentile, the 50th percentile (median), and the 75th percentile, respectively. See text for details.

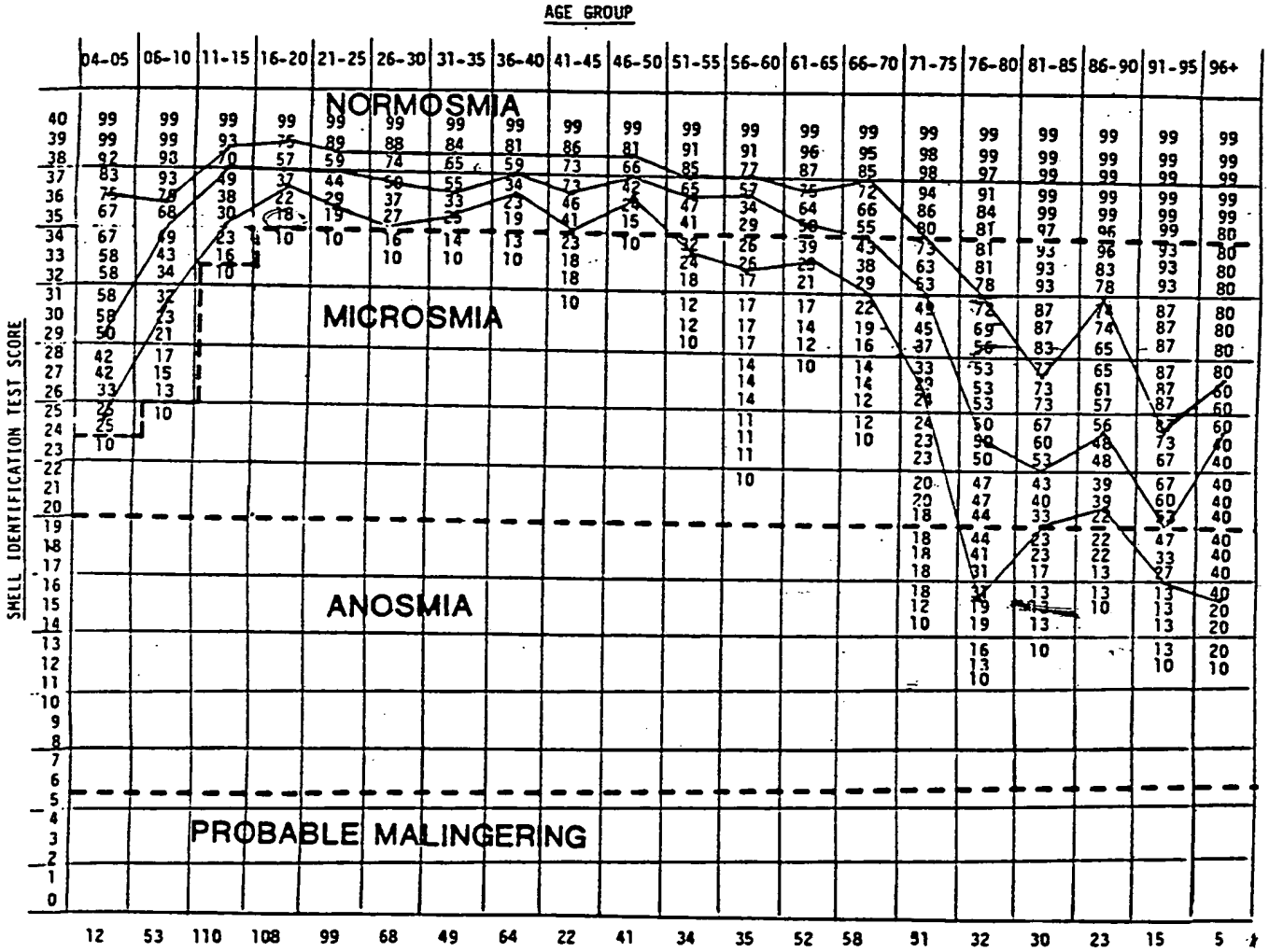
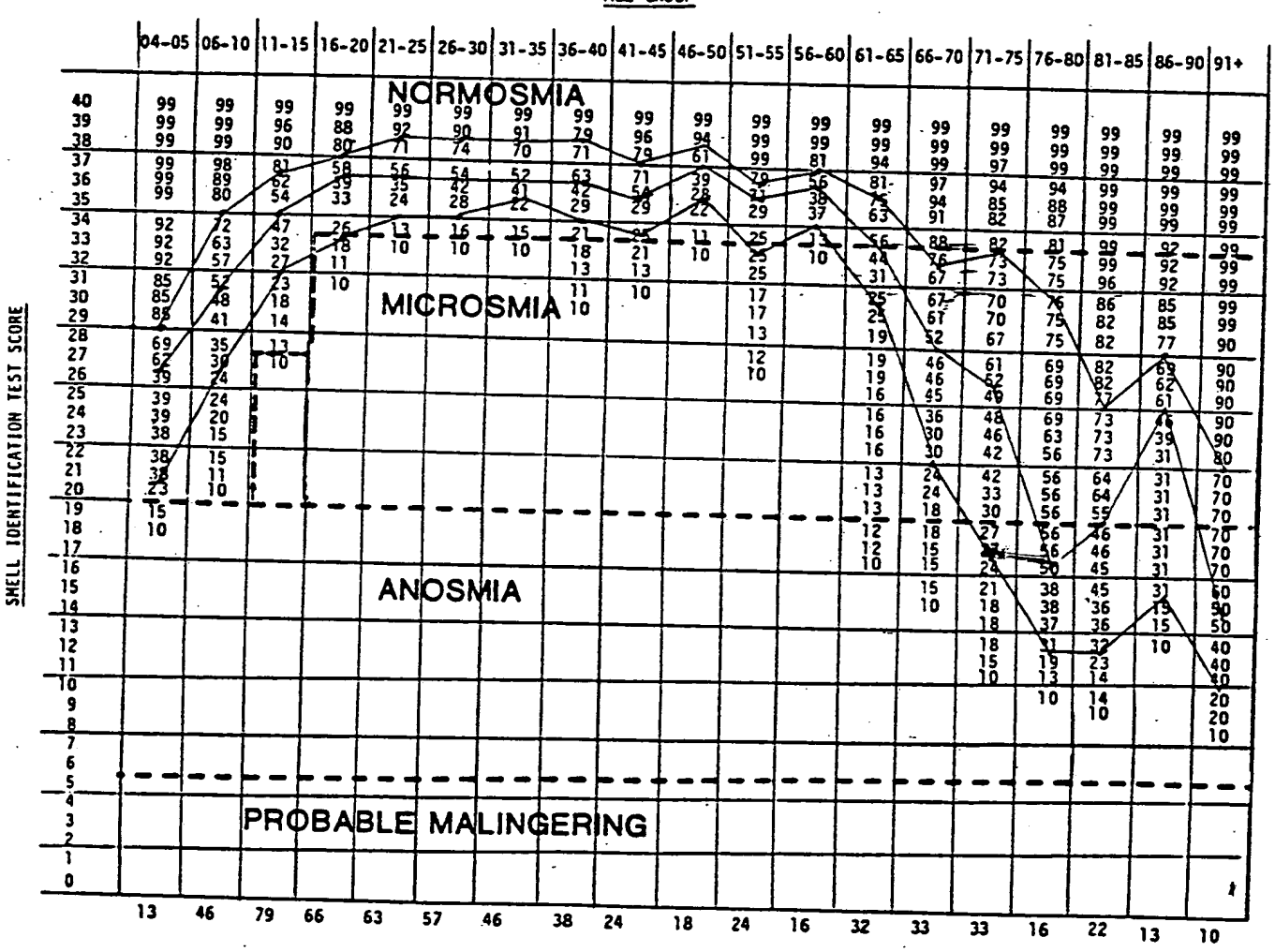


Table 2: Percentile Table for Males (N = 649). Numbers in body of table are percentile scores corresponding to Smell Identification Test™ scores in each age category. Numbers at bottom of table refer to sample sizes within each age category. The three solid lines crossing the columns of percentile scores represent, from bottom to top, the regions of the 25th percentile, the 50th percentile (median), and the 75th percentile, respectively. See text for details.



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C

☐ 1: J Agric Food Chem 2001 Oct;49(10):4813-7

ACS PUBLICATIONS

Aromatic profile of aqueous banana essence and banana fruit by gas chromatography-mass spectrometry (GC-MS) and gas chromatography-olfactometry (GC-O).

Jordan MJ, Tandon K, Shaw PE, Goodner KL.

U.S. Citrus and Subtropical Products Laboratory, Agricultural Research Service, U.S. Department of Agriculture, 600 Avenue S, N.W., Winter Haven, Florida 33881, USA.

Gas chromatography-mass spectrometry (GC-MS) and gas chromatography-olfactometry (GC-O) were used to determine the aromatic composition and aroma active components of commercial banana essence and fresh banana fruit paste. Totals of 43 and 26 compounds were quantified in commercial banana essence and fresh banana fruit paste, respectively. Five new components in commercial banana essence were identified as methyl butyrate, 2,3-butanediol diacetate, 2-hydroxy-3-methylethylbutyrate, 1-methylbutyl isobutyrate, and ethyl 3-hydroxyhexanoate. A total of 42 components appear to contribute to the aromatic profile in banana. Isoamyl acetate, 2-pentanol acetate, 2-methyl-1-propanol, 3-methyl-1-butanol, 3-methylbutanal, acetal, isobutyl acetate, hexanal, ethyl butyrate, 2-heptanol, and butyl butyrate had high concentrations and were most detected by GC-O panelists in the commercial banana essence. Volatile components found only in fresh banana fruit paste that were detected by aroma panelists include E-2-hexenal, limonene, and eugenol.

PMID: 11600027 [PubMed - indexed for MEDLINE]

☐ 1: J Agric Food Chem 2002 Mar 27;50(7):2016-21

ACS PUBLICATIONS

Identification and quantification of aroma-active components that contribute to the distinct malty flavor of buckwheat honey.

Zhou Q, Wintersteen CL, Cadwallader KR.

Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, USA.

Characteristic aroma components of buckwheat honey were studied by combined sensory and instrumental techniques. Relative aroma intensity of individual volatile components was evaluated by aroma extract dilution analysis (AEDA) of solvent extracts and by gas chromatography-olfactometry (GCO) of decreasing headspace samples (GCO-H). Results indicated that 3-methylbutanal, 3-hydroxy-4,5-dimethyl-2(5H)-furanone (sotolon), and (E)-beta-damascenone were the most potent odorants in buckwheat honey, with 3-methylbutanal being primarily responsible for the distinct malty aroma. Other important aroma-active compounds included methylpropanal, 2,3-butanedione, phenylacetaldehyde, 3-methylbutyric acid, maltol, vanillin, methional, coumarin, and p-cresol.

PMID: 11902950 [PubMed - indexed for MEDLINE]

E

Oklahoma Cooperative Extension Service
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Measuring Farmstead Odors

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The nose and the brain work together to create what we perceive as odor. Our sense of smell is activated when the nose captures odor-causing chemicals, called odorants, from the air. Nerves located in the nose pass a message on to the brain when they detect an odorant. The brain then analyzes the message about the odorant.

Scientists have identified hundreds of odorants forming the collection of smells known as farmstead odors. Table 1 is a partial list of the groups of odorants released by animals and by breakdown of manure. Under each group is a list of individual chemical compounds that are commonly found in manure odors.

Odor Perception: Detection, Recognition, and Notes

The brain makes decisions about the odorant at certain concentrations. In Table 1, two numbers are listed next to the odorants; these are the detection and recognition levels for the odorants. The first number, the detection level, is the concentration in parts per billion (ppb) at which the average, healthy person first notices an odor. People cannot recognize the odor at the **detection level,** but they know they smell "something." For example, the brain notices an odor when there are 17 parts of ammonia in one billion parts of air. The second number is the **recognition** level. At this concentration, the brain begins to recognize the odorant as a distinct scent. The average human recognizes the scent of ammonia cleanser when the concentration of ammonia gas reaches 37,000 parts per billion.

Values for detection and recognition levels can be slightly difficult to comprehend. Let's look at a few examples. A person is standing on the floor of the Louisiana Superdome. The Superdome, a very large building, contains 125 million cubic feet of air space. In metric units, this equals 3.5 billion liters. Now, let's release hydrogen sulfide into the Superdome. The detection level of hydrogen sulfide given in Table 1 is 0.5 ppb. Although hydrogen sulfide is a gas, it has a weight based on the size of its molecule. A person would smell "something" if one tenth of an ounce of hydrogen sulfide were mixed in with clean air in the Superdome. The recognition level for hydrogen sulfide is 4.7 ppb. The brain would begin to recognize a faint rotten egg smell if one ounce of hydrogen sulfide was released. Skatole is a large nitrogen-containing compound largely responsible for making manure smell like manure. Skatole's detection level is 1.2 ppb, or less than one ounce of skatole in the Superdome. The recognition level of skatole is

470 ppb; therefore, the brain would not recognize a manure-like smell until about 20 pounds of skatole were released into the building.

From the previous two examples, you can see that detection and recognition levels are not always directly related. Humans can detect and recognize hydrogen sulfide at very low levels. Skatole, on the other hand, is easily detected, but only becomes recognizable at larger doses. Ammonia is an extreme example. The average human would notice "something" in the Superdome if two ounces of ammonia gas were released. They would not recognize it as ammonia until nearly 220 pounds were added!

Farm odors are never pure samples of one odorant, but rather a mixture of many different odorants. Recently, a sample of air was taken from a hog building in Germany. When chemists analyzed the sample, they measured at least 11 different organic acids, but none of the individual acids were present at detectable levels. Because the individual odorants were below the detection level does not mean they could not be smelled. The brain lumps similar odorants together as a group. You would smell something in the barn, because your sense of smell lumps all 11 organic acids together into a composite, "sour meat" smell.

Perfumers and people who blend odors call a group of odorants making a distinct scent an odor note. Let's go back to the Superdome to illustrate odor notes. If you are standing in the middle of the football field, you may not hear one person way up in the stands blowing softly into a plastic trumpet. If a hundred people blow into plastic, brass, and tin trumpets all at the same time, you will definitely hear a "note."

Odor Concentration

Farmstead odors always occur as mixtures of odorants. It is difficult and expensive to measure the concentration of each odorant in a sample. Instead, odor scientists measure the concentration of odors as a whole by grabbing a sample and presenting it to a panel of trained sniffers. The sample is diluted with odorless gas until half of the panel can no longer smell anything. When 50 percent of the sniffers can no longer detect an odor, we say the sample has been diluted to the **detection threshold**. Detection threshold is similar to detection level discussed in the previous sections. Detection threshold is the detection level of a mixture of odorants at the conditions given in the experiment.

The ratio of odorless gas to sample is called the dilution factor. **Dilution factor** is a good measure of odor concentration. The odor threshold standard used by the European Union gives odor concentration at the detection threshold the arbitrary value of one odor unit per cubic meter (OU/m^3). For example, an air sample taken from inside a dairy barn is diluted 100 times until half of the people on a panel could no longer detect an odor. The air inside the dairy barn has an odor concentration of 100 OU/m^3. Other odor threshold standards do not state odor concentration in odor units per volume. Since the dilution factor is a ratio, it has no units; therefore, the inverse of dilution factor is simply given the units OU. No matter what standard you use, the concept is the same: dilute the sample to the detection threshold, then use the inverse of dilutions as odor concentration.

Table 1. Components of Manure Odors.

Groups and Individual Odorants	Detection Level (ppb)	Recognition Level (ppb)	Odor Description
Organic Acids			

Acetic Acid	10.2	1,000	Vinegar
Propionic Acid	3.6	300	
Butyric Acid	1.1	1	Sour Meat
Iso-Valeric Acid	1.2	-	
Valeric Acid	-	20	
Alcohols, Aldehydes, Ketones			
Methanol	-	100,000	Sweet
Formaldehyde	-	1,000	Straw, pungent
Acetylaldehyde	-	210	Fruity, pungent
Acetone	4.0	100,000	Sweet, pungent
Methyl Ethyl Ketone	-	10,000	Sweet
Phenolic Compounds			
Phenol	5.7	1,000	Medicinal
p-Cresol	8.0	-	
Nitrogen Compounds			
Ammonia	17	37,000	Sharp, pungent
Methylamine	-	2.1	Fishy, pungent
Dimethlyamine	37	37	Fishy, pungent
Diethylamine	-	500	Fishy, pungent
Indole	1.0	-	Fecal
Skatole	1.2	470	Fecal, pungent
Sulfur Compounds			
Hydrogen Sulfide	0.5	4.7	Rotten Egg
Methyl Mercaptan	0.5	2.1	Rotten Cabbage
Dimethyl Sulfide	1.1	1.1	Rotten Vegetable
Diethyl Sulfide	6.0	6.0	Rotten Vegetable

Odor Character

We use the term character to describe what an odor smells like. Odor character does not change with concentration. Ammonia at 10 OU/m^3 smells the same as ammonia at 100 OU/m^3. The fourth column of Table 1 lists identifying terms used to describe the character of selected odorants. Some of the descriptive words listed in Table 1 conjure up pleasant responses. Many alcohols and ketones have "sweet" and "fruity" descriptors. Farmstead odors are mixtures of many odorants. What is pleasant by itself may be unpleasant when mixed with other compounds. In addition, unpleasant odors often add a tinge or edge to a pleasant smelling mixture. Surprisingly, indole, a nitrogen-containing compound described in Table 1 as having a "fecal" odor, is a major component in jasmine-scented perfumes.

Odor character is subjective or qualitative. In other words, it is difficult to assign a number to character. Two methods to quantify or assign a numerical value to odor character are by offensiveness and by hedonic tone.

Offensiveness

It is difficult to say exactly what farmstead odors smell like, and in the final analysis, the exact description of the smell may not matter. People know if they like the smell or not. Offensiveness is an attempt to add degrees of good and bad to "yes, it smells good - no, it smells bad" phenomena. The procedure involves three steps: an odor panel measures offensiveness; a series of samples is diluted to equal odor strength or intensity; and panelists are asked to rank the offensiveness of each sample on a scale of 0 to 5 (0 = inoffensive, 5 = strongly offensive).

Hedonic Tone

Hedonics is the science of comparisons. Odor panelists compare an unknown sample to a set of known odorants. The panel decides which of the known odorants best describe the odor. The odor is assigned a rating, called the hedonic tone, based on the comparisons. Hedonic tone provides a sense of the relative pleasantness of a sample. Pleasant odors have positive hedonic tones, and negative hedonic tones indicate unpleasant odors. Table 2 lists hedonic tones for common agricultural odors as well as some of the odorants listed in Table 1. If dead animal scent has a hedonic tone of -3.75, and rotten fruit -2.76, we can assume most people find rotting animal flesh more offensive than rotting fruit.

Table 2. Hedonic Tone of Common Agricultural Odors.

Odor	Hedonic Tone
Strawberry	2.93
Apple	2.61
Hay	1.30
Grain	0.63
Mushroom	0.52
Isovaleric Acid	-1.57
Butanoic Acid	-1.77
Mercaptans	-2.30
Ammonia	-2.47
Rotten Fruit	-2.76
Urine	-3.34
Manure	-3.36
Dead Animal	-3.75

Odor Intensity

Offensiveness tells us how bad an odor smells, and concentration gives us an idea how many molecules of odorants are floating in the air, but neither measure tells how strong an odor smells. For that, we need a third measure - odor intensity. Odor intensity is the direct measurement of a person's reaction to an odor. To measure odor intensity, scientists ask a panel to describe the strength of an unknown odor without knowing the odor concentration or dilution factor. A commonly used scale ranks intensity between 0 and 6 (0 = no odor, 6 = extremely strong odor).

Intensity experiments usually attempt to determine the relationship between concentration and intensity. An original sample of odorous gasses is mixed with clean

air in a series of dilutions and presented to a panel. Figure 1 shows the results of a series of dilutions performed on two common sources of farmstead odors - chicken house exhaust and liquid hog manure. These results demonstrate three concepts needed to understand intensity.

First, every mixture of odorants has its own relationship between concentration and intensity. Similar mixtures of odorants, such as five different samples of chicken house exhaust, have similar concentration-intensity relationships. Second, intensity and concentration are not a one-to-one relationship. If you dilute an odor sample in half, the odor intensity is not diminished by one half. In order to diminish a strong chicken house odor (I = 4) to a faint odor (I = 2), we would have to dilute a 40 OU/m^3 sample down to 5 OU/m^3. This is an 8-fold dilution.

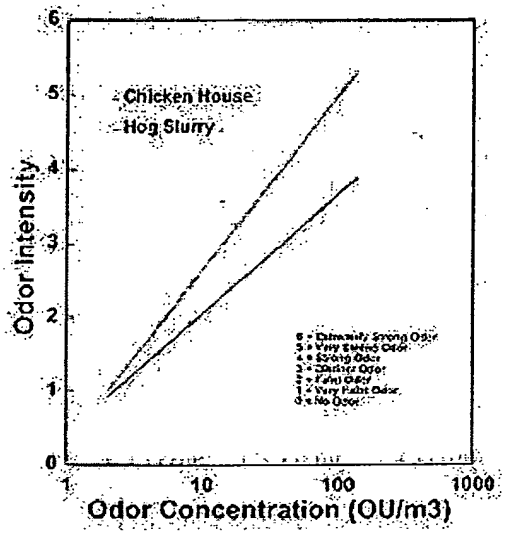

Figure 1. Relationship of Odor Intensity and Odor Concentration.

Third, intensity and character are not related. According to the results shown in Figure 1, if odor concentrations are held equal, the panel would say chicken house odor is more intense than hog slurry odor. This does not mean the chicken house smells worse than the hog slurry; it only means the chicken house smells stronger than the hog slurry. Complete description of an odor involves measuring both intensity and character. Perfumes give off high-intensity odors, but these odors are not offensive. An apple pie baking in the oven smells both strong and pleasant. Skunks release strong and offensive odors. A glass of water smells neither strong nor offensive because it has no smell at all.

Odor Persistence

Perfumers are masters in the art of blending many odors to form complex mixtures known as perfume. If one distinct odor is a note, then a mixture of many odors is a chord. Perfumers also recognize that a chord of odors can change with time. Perfumers group notes according to their relative volatility or persistence. The most persistent odors are base notes. The least persistent odors are top notes. Odorants with medium volatility are called middle notes or modifiers. When perfume is placed on the skin, the first scent smelled is the top note. Since top notes are made of volatile (or short-lived) odorants, they fade with time. Base notes remain long after the top notes have faded. Middle notes give the perfume "lift" or "body" throughout the life of the scent.

Table 3. Likely Grouping of Manure Odor Notes

Based on Relative Volatility of Odorants.

Top Notes	Middle Notes	Base Notes
Hydrogen sulfide	Aldehydes	Organic Acids
	Alcohols	Phenolic Compounds
Ammonia	Ketones	
	Amines	Indole and Skatole
	Mercaptans	Organic Sulfides (more than 5 carbons)
	Organic Sulfides (2 to 4 carbons)	Dust borne odorants

Farmstead odors are also chords of many notes. Odorants in the manure chord can be grouped in notes based on relative volatility. Table 3 classifies common manure odorants into top, middle, and base notes. Knowing that all notes do not have the same persistence can explain why the strength of farmstead odors changes over time. Consider the results shown in Table 4 from a study conducted in England. Different types of swine waste were applied 0.2 inches deep to soil inside a wind tunnel. Samples of air were collected and presented to a panel to determine odor offensiveness, concentration, and intensity immediately after spreading, and again four to six hours after application. Let us look at the results of this experiment as if the swine waste were perfume. The panel decided raw manure was definitely offensive. Odor intensity was extremely strong directly after applying raw manure, and intensity remained extremely strong six hours after application. The odors released by raw manure exposed at the soil contained persistent, strong-smelling odorants. Using perfume terminology, raw waste is heavy on the base notes.

Anaerobically digested manure paints a different picture. Anaerobically digested manure was described by the panel as faintly offensive. Initial intensity was extremely strong Ðas it was for the raw manure. Odors from anaerobically digested manure did not persist, however. Six hours after application, the panel smelled only faint odors in the samples. This means the anaerobically digested manure contained more top notes and less base notes. These results are consistent with the chemistry of anaerobic digestion. During digestion base notes (organic acids, skatole, and large organic sulfides) are converted to top notes (hydrogen sulfide, and ammonia) and odorless gases (carbon dioxide, methane).

Treating the raw manure by aeration reduced odors even further than anaerobic treatment. The panel described screen manure aerated at 1 to 2 mg/l dissolved oxygen as inoffensive. Why did land application odors increase with time? Why did they rise from no odor right after application to a faint odor four hours later? Aerobic bacteria are produced as raw manure is aerated, creating a large, living biomass. The aerobic biomass dies when exposed to a new environment by land application. The biomass decays anaerobically - releasing odorants similar to anaerobically digested manure.

Table 4. Odor Offensiveness, Concentration and Intensity of Land Applied Swine Wastes Based on Wind Tunnel Experiments in England.

Type of Waste	Offensiveness	Highest Measured Odor Concentration (OU/m3)		Highest Measured Odor Intensity	
		Initial	*After 4-6 hours*	*Initial*	*After 4-6 hours*
Raw Manure	Definitely Offensive	1740	320	Extremely Strong Odor	Extremely Strong Odor

Raw Manure Passed Through Screen	Definitely Offensive	250	190	Extremely Strong Odor	Extremely Strong Odor
Raw Manure Stored 14 days	Faintly Offensive	460	60	Very Strong Odor	Distinct Odor
Anaerobically Digested Manure	Faintly Offensive	350	45	Extremely Strong Odor	Faint Odor
Anaerobically Digested Manure Stored 14 days	Faintly Offensive	83	39	Strong Odor	Distinct Odor
Screened Manure Aerated at Low Dissolved Oxygen	Faintly Offensive	280	100	Distinct Odor	Faint Odor
Screened Manure Aerated at 1-2 mg/l Dissolved Oxygen	Inoffensive	60	61	No Odor	Faint Odor

Methods of Odor Measurement

Scentometer

A scentometer is a simple, hand-held odor dilution device used to measure odor concentration in the field. The person taking measurements holds the device up to his nose and breaths through the scentometer. Gases can either pass directly to the nose or pass through an activated carbon filter. The analyst chooses dilution factor by selecting the size of the hole passing unfiltered air. Advantages of the scentometer are its portabilty, its simplicity of use, and its ability to give immediate values for odor concentration and intensity. It is particularly useful for measuring intensity of odor sources. The main disadvantage is that it is difficult to overcome the analyst's personal bias in measurement. Also, the analyst's ability to distinguish odors diminishes the longer he is exposed to odors. Scentometer readings taken after an hour of sniffing may vary from readings taken when first arriving at the farm.

Olfactometer

An olfactometer is a laboratory device that distributes sample dilutions to odor panelists. A sample is collected at the farm and stored in a teflon or kevlar bag and brought into the laboratory. There are a number of variations on the olfactometer, but all devices do the same thing: the original sample is diluted with a stream of odorless gas and presented to a sniffer. Olfactometry is used to measure odor concentration, intensity, and offensiveness. Flexibility of use is the main advantage. Disadvantages are expense of operation and difficulty collecting representative samples of odorous gas.

Electronic Nose

Electronic noses mimic the human olfactory system using polymer sensors to simulate receptors in the nose and a computer to simulate the brain. Chemical composition of sensors is altered so each sensor responds differently to a given odorant. The main use of an electronic nose is to compare differences between mixtures of odors. The primary drawback is the electronic nose must "learn" a pattern of sensor responses before it can make future comparisons. Work is underway to devise electronics that will allow the nose to "guess" new odors. If properly trained, electronic noses may prove valuable in measuring odor character. A second drawback is, at the current level of technology; electronic noses are not sensitive at low odor concentrations.

Chemical Methods

Chemical methods are used to determine the actual concentration of individual odorants in a sample taken from the field. The most common instrument used in odorant analysis

is a gas chromatograph with a mass spectrometer detector. Like the electronic nose, a gas chromatograph distinguishes compounds by comparing to a reference standard. The main drawback to chemical methods is the shear number of potential odorants needed to analyze in a single sample of farmstead odors.

F-1740, Measuring Farmstead Odors *(pdf file)*

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Modification is a perceptual phenomenon. Although the chemical mixtures that are used to change odor perception usually do not react outside of the olfactory organ, modern theory does postulate that chemical complexes involving enzymes are active within the organ. Changes in the way these complexes form may explain why mixtures of odorants vary from individual chemicals in the way they are perceived.

Odors and Their Mixtures

Odor is that property of a substance that makes it perceptible to the sense of smell. Although it is certain that odor is caused by molecular structure, there remains little predictability about this correlation of odor with structures. It is known from experience that certain chemical classes have certain types of odor (see also Flavor characterization), but even an expert cannot predict what an unfamiliar molecule or mixture will smell like.

Intensity perception. The measurable properties of odor perception are its intensity and its character. The measurement and expression of odor mixture intensity can be achieved in a number of ways, but they are almost all subjective. The simplest but the most subjective method is the use of a hedonic scale. The format possibilities are many, eg, 0 = no odor, 1 = barely perceptible, 2 = distinct, 3 = strong, 4 = very strong, and 5 = overpowering.

One of the most objective measures of an odorant's intensity is its threshold which, however, reflects the intensity of only one specific odorant concentration, ie, the weakest that can be detected.

All the senses, including smell, relate to the psychophysical law (Stevens' law) as expressed by the power equation:

$$\psi = k\phi^{\beta}$$

where ψ is the perceived intensity of the sensation, ie, the odor; k is a constant; and ϕ is the physical intensity of the stimulus, ie, the odorant. Generally, the sensation varies as a power function of the stimulus. In olfaction, the power β is less than one.

Character perception. Odor character is purely subjective. Several chemicals have been experimentally characterized by scaling the degrees to which each chemical possesses subjective reference qualities, eg, burnt, fruity, and spicy. But no method exists that can reliably characterize odors.

Mixture perception (modification). Many odorous and nonodorous chemicals are used to control odors, but only those that work essentially by altering the way the nose perceives the character and intensity are true odor modifiers.

Products

Although the original intent of deodorizers was to reduce malodor, use for decorative purposes is becoming an important factor. The active ingredient of masks and counteractants are oils: essential oils, which are fragrance extracts from flowers, herbs, fruits, and trees; animal extractives; and aroma chemicals, which may be either natural or synthetic.

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Ann. N.Y. Acad. Sci. 237, 1 (1974); H.R. Moskowitz and C.L. Gerbers, p. 1.
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OIL SANDS. See Tar sands.

OILS, ESSENTIAL

A simple, though incomplete, definition of essential oils is the following: an essential oil is the predominantly volatile material isolated by some physical process from an odorous single-species botanical. Over 3000 oils have been identified from the vast number of plant species and several hundred have been commercialized. Of these, some are extremely rare and produced in only kilogram quantities, eg, violet oil, concretes (flower extracts), and angelica root oil.

Essential oils are now generally manufactured close to the growing area. Product quality has suffered; however. Essential oils are easily adulterated and this technology has not been overlooked by isolated local producers.

Essential oils are isolated from various plant parts, such as leaves (patchouli), fruit (mandarin), bark (cinnamon), root (ginger), grass (citronella), wood (anyris), heartwood (cedar), gum (myrrh), balsam (tolu balsam), berries (pimenta), seed (caraway), flowers (rose), twigs (clove stems), and buds (cloves). These plant parts are processed to yield their quintessences or essential oils, which are mostly devoid of cellulose, glycerides, starches, sugars, tannins, salts, and minerals which also occur in these botanicals.

The common physical method for isolating essential oils from the botanical is steam distillation, wherein small amounts of nonvolatiles may be carried over. Some oils are expressed. Many flower oils are extracted with a purified petroleum solvent.

Essential oils are generally liquid at room temperature; however, some are semisolid, such as *Mentha arvensis* (Brazilian mint), and several are solid, eg, oil of guaiac wood.

The cultivation of essential oil-bearing plants has kept pace with modern agricultural methods. Hybrids are grown to yield oils of specific odor, flavor, or properties.

Essential oils are used as such for flavors and fragrances, but products derived from, or based on essential oils have large volume usage for specific applications. Essential oils are concentrated, rectified, extracted, or chemically treated to further isolate vital components, purify, adjust properties, or increase the concentration of significant flavor or fragrance components (see Flavors and spices; Perfumes).

Composition

The volatile components of essential oils usually contain fifteen carbon atoms or less. However, seed oils contain long-chain fatty acids or esters and even glycerides that are carried over in distillation; the amounts of these components are very low.

Essential oils basically are made up of carbon, hydrogen, and oxygen, and occasionally nitrogen and sulfur. The largest class of components is the terpenes which have ten carbon atoms and are head-to-tail condensation products of two isoprene molecules (see Terpenoids). The terpenes may be aliphatic, alicyclic, or bi- and tricyclic of varying degrees of unsaturation up to three double bonds.

It is not uncommon for an essential oil to contain over two hundred components and often the trace substances (in ppm) are essential to the odor and flavor. The absence of even one component may change the aroma. The same species of botanical, grown in different parts of the world, usually has the same components; however, climatic and topographical conditions affect plants and can alter the essential oil quantitatively, but rarely qualitatively.

Production

In the botanical, the essential oil is present in oil sacs. It is isolated by comminution, and the action of heat, water, and solvents.

Steam distillation. Steam or hydrodistillation is the preferred method for producing essential oils, employing either water, wet steam, or steam.

Extraction. An essential oil that is sensitive to heat, eg, jasmine or tuberose, or contains an essential nonvolatile constituent, eg, piperine in black pepper, is extracted with a solvent (see Extraction).

Synthetic Substitutes for Essential Oils

Fluctuations in the cost and availability of natural oils and the high cost of some oils have induced users to seek substitutes. Several former large-volume oils have been replaced by synthetics because of large volume demands. The expensive variations in cost are especially evident in essences such as rose, jasmine, violet, lilac, neroli, etc. Duplication of these items is economically worthwhile. Modern techniques and instru-

mentation offer the possibility for total analysis of these oils. This route has been undertaken by the primary fragrance and flavor companies throughout the world in the attempt to find economic and available substitutes. Nonetheless, there is a trend away from synthetic oils because complete duplications are in most cases not technically, aesthetically, or economically possible.

Health and Safety Factors

Most essential oils, since they are natural and have a history of use, are considered GRAS (generally recognized as safe) by the FDA. Safety and toxicity testing and evaluations and regulations are different for food additives than for fragrance oils and cosmetics (qv). Some oils can be used for both purposes, including celery, rose, and black pepper. Some oils, such as cinnamon oil, can be used in flavors, but not in fragrances because of skin irritation.

Commercial Essential Oils

The commercial essential oils include allspice (pimenta berry), bitter almond, amyris, anise, star anise, sweet basil, bay (myrcia), bergamot, sweet birch, bois de rose (rosewood), camphor, cananga, caraway, cardamom, cassia, cedarwood, cinnamon, citronella, clove, coriander, eucalyptus, geranium, ginger, grapefruit, jasmine, juniper, labdanum, lavandin, lavender, lemon, distilled lime, japanese mint, neroli, nutmeg, ocotea, bitter orange, sweet orange, origanum, orris root, palmarosa, patchouli, black pepper, peppermint, petitgrain bigarade, pine, pinus pumilio, rose, rosemary, dalmatian sage, sage clary (sage muscatel), East Indian sandalwood (santal), spearmint, spike lavender (spike), thuja (cedarleaf), thyme, turpentine, vetiver, wintergreen, and ylang ylang.

JAMES A. ROGERS, JR.
Fritzsche, Dodge & Olcott, Inc.

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OIL SHALE

Oil shale consists of a marlstone-type sedimentary inorganic material that contains complex organic polymers that are high molecular weight solids. The organic kerogen is a three-dimensional polymer, insoluble in conventional organic solvents, and associated with small amounts of a benzene-soluble organic material, bitumen. Oil-shale deposits were formed in ancient lakes and seas by the slow deposition of organic and inorganic remains from the bodies of water. As the waters stagnated and dried, the deposits compacted. The geology and the composition of inorganic and organic components of oil shale varies with deposit location.

Reserves

Oil-shale deposits occur widely throughout the world; estimates of the resources by continent are given in Table 1. Characteristics of many of the world's best-known oil shales are summarized in Table 2. Oil-shale deposits in the United States occur over a wide area. The most extensive deposits, which cover ca 647,000 km^2 (250,000 mi^2), are the Devonian-Mississippian shales of the eastern United States. The richest U.S. oil shales are in the Green River formation of Colorado, Utah, and Wyoming.

Retorting

Thermal decomposition of oil shale. The thermal decomposition of oil shale, ie, pyrolysis or retorting, yields liquid, gaseous, and solid products. The liquid, which is produced by pyrolysis, is in the form of a vapor or mist. The remaining organic carbon remains on the retorted shale, the mineral matter, as a cokelike deposit. The amounts of oil, gas, and coke which ultimately are formed depend on the heating rate of the oil shale and the temperature–time history of the liberated oil.

Table 1. Shale-Oil Resources of the Populous Land Areas, 10^9 m^3[a]

Shale-oil yield range, L/t[c]	Total resource[b]			Known resources: marginal or submarginal recovery			Recoverable known resources
	21–42	42–104	104–417	21–42	42–104	104–417	42–417
Africa	71,500	12,700	636	small	small	14	1.6
Asia	93,800	17,500	874	na	2	11	3.2
Australia and New Zealand	15,900	3,200	159	na	small	small	small
Europe	22,260	4,100	223	na	1	6	4.8
North America	41,400	8,000	477	350	254	99	13
South America	33,400	6,400	318	na	119	small	8
Total	*278,260*	*51,900*	*2,687*	*350*	*376*	*130*	*30.6*

[a] To convert m^3 to bbl, divide by 0.159.
[b] Includes oil shale in known resources, in extensions of known resources, and in undiscovered but anticipated resources.
[c] To convert L/t to gal/short ton, multiply by 0.2397.

Table 2. Properties of Oil Shales

	Australia (Glen Davis)[a]	Brazil (Tremembe-Taubate)[a]	Canada (Nova Scotia)[b]	Manchuria (Fushun)[b]	New Zealand (Orepuki)[b]	South Africa (Ermelo)[a]	Spain (Puertollano)[a]	United States (Colorado)[a]
Modified Fischer assay								
oil, L/t[c]	414	156	257	38	331	228	234	122
oil, wt%	30.0	11.5	18.8	3.0	24.8	17.6	17.6	9.3
water, wt%	0.7	6.2	0.8	4.9	8.3	3.0	1.8	1.0
spent shale, wt%	64.1	78.4	77.7	90.3	57.6	75.6	78.4	87.5
gas and loss, wt%	4.3	3.9	2.7	1.8	9.3	3.8	2.2	1.6
conversion of organic material to oil,[d] wt%	66	59	60[e]	33	45	34	57[e]	70
Rock characteristics								
sp gr (at 16°C)	1.60	1.70		2.29	1.46	1.58	1.80	2.23
heating value, MJ/kg[f]	18.8	8.2	12.6	3.4	21.3	19.1	12.5	5.1
ash, wt%	51.6	71.4	62.4	82.7	32.7	42.5	62.8	66.9
organic carbon, wt%	39.8	16.5	26.3	7.9	45.7	43.8	26.0	11.3
Assay oil								
sp gr (at 16°C)	0.89	0.88	0.88	0.92	0.90	0.93	0.90	0.91
carbon, wt%	85.4	84.3		85.7	83.4	84.8		84.6
hydrogen, wt%	12.0	12.0		10.7	11.8	11.1		11.6
nitrogen, wt%	0.5	1.1			0.6		0.9	1.8
sulfur, wt%	0.4	0.2			0.6	0.6	0.3	0.5
Ash analysis, wt%								
SiO_2	81.5	55.8	61.1	62.3	44.2	61.3	56.6	43.6
Al_2O_3	10.1	26.7	30.1	26.7	28.1	30.5	27.6	11.1
Fe_2O	3.0	8.5	5.0	6.1	20.5	2.9	9.1	4.6
CaO	0.8	2.8	1.1	0.1	4.6	1.6	2.6	22.7
MgO	0.8	3.7	1.6	1.8	1.4	1.7	2.2	10.0
other oxides	3.8	2.5	1.1	3.0	1.2	2.1	1.9	8.0

[a] Average sample.
[b] Selected sample.
[c] To convert L/t to gal/short ton, multiply by 0.2397.
[d] Based on recovery of carbon in oil from organic carbon in shale.
[e] Carbon content of oil ca 84 wt%.
[f] To convert MJ/kg to Btu/lb, multiply by 430.4.

Numerous kinetic mechanisms have been proposed for oil-shale pyrolysis reactions. The kinetics appear to be adequately represented by first-order rate mechanisms, eg,

$$\text{kerogen} \xrightarrow{k_1} \text{bitumen} + \text{gas} + \text{coke}$$

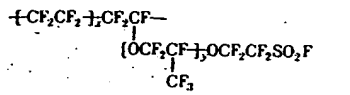
$$\text{bitumen} \xrightarrow{k_2} \text{oil} + \text{gas} + \text{coke}$$

Most oil-shale retorting processes are carried out at ca 480°C to maximize liquid-product yield.

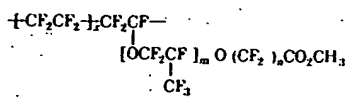
Aboveground retorting. The first aboveground oil-shale processes were batch or semibatch, and modern commercial contenders are continuous in both feed and product removal. Room-and-pillar mining is used for commercial aboveground retorts. Open-pit mining has the potential for greater resource recovery but requires off-site spent-shale disposal.

The heat required for retorting is transferred to the oil shale in four main types of retorts. In Type-1 retorts, the heat must be transferred through the vessel wall to the oil shale. A combustion zone within the

new electrolytic process for chlor-alkali production using perfluorinated ion-exchange membranes (see Alkali and chlorine products). Flemion is a carboxylic acid type. The different ion-exchange groups greatly affect membrane properties.



Nafion polymer



(m = 0 or 1, n = 1–5)
Flemion polymer

Both polymers are melt-processable and can be fabricated into films by extrusion-molding. These films can be easily converted to the corresponding ion-exchange membrane by alkaline hydrolysis.

Preparation

The general procedure includes synthesis of a perfluorovinyl ether moiety with a functional group, its copolymerization with tetrafluoroethylene in the presence of a radical initiator in an aqueous or inert organic medium, and the formation of a membrane.

Fabrication. The crystallinity of the copolymer depends upon the content of the functional conomonomer. Amorphous or partly crystalline copolymers are fabricated into films (100–250 μm thick) with conventional extrusion techniques. The films are usually reinforced with Teflon cloth and converted to sulfonic- or carboxylic-acid-type ion-exchange membranes by alkaline hydrolysis.

A sulfonic acid group can be converted to a carboxylic acid group:

$$\cdots -O(CF_2)_nSO_2X \rightarrow\rightarrow \cdots -O(CF_2)_{n-1}CO_2H$$

(X = Cl or F)

The sulfonyl halide group is converted to sulfinic acid by reduction and then the carboxylic acid group, having one CF_2 less than the original chain of sulfonic acid, is formed through a desulfonylation reaction.

Applications

In the electrolysis of brine, a cation-exchange membrane is used. DuPont has developed a variety of Nafion series. The Nafion 300 series produces 10–20% caustic soda. For the production of 20–28% caustic soda, the Nafion 200 series was developed. The Nafion 900 series membranes are carboxylate–sulfonate two-layer membranes with ca 95% current efficiency at 33% caustic soda.

Asahi Glass has developed the Flemion series. For the production of 5% caustic soda, a standard Flemion 230 is used advantageously with a current efficiency of 94%. With the Flemion 700 series, gas bubbles can be removed easily from the membrane surfaces.

A new electrolytic process with a zero-gap cell, called the AZEC system, combined with Flemion 723 or 753 and a new electrode system, has resulted in drastic reductions in energy consumption.

Asahi Chemical Tokuyama Soda improved the electrolytic performance of Nafion-type membranes by chemical modification of the cathode-side surface of the carboxylic acid-type membrane.

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PERFLUORO COMPOUNDS. See Fluorine compounds, organic.

PERFUMES

Perfumery is the art of producing fragrances through the combination of odoriferous substances. The word perfume is derived from the Latin meaning "through smoke". Throughout history, perfumes have played an important role in human lives, and have been associated with notions of happiness, beauty, and satisfaction. Until this century, fragrance materials have been derived from natural sources, which has placed limitations on odor types and markets (see also Cosmetics; Odor modification). The increased use of perfumes in the last thirty years would have been impossible without the development of the chemistry that allowed the invention of totally new odoriferous molecules as well as the synthesis of natural ones. Fragrances are no longer a luxury for the rich but today are incorporated routinely in a great number of products that are in daily use.

Fragrance Raw Materials

Natural products. Essential oils are volatile materials produced from odorous plant material, generally by water or steam distillation or by expressing (see Oils, essential).

A concrete is an extraction almost exclusively from vegetable origin such as leaves, bark, flowers, and fruit. This is normally obtained by extraction with hydrocarbon solvents.

Absolutes are the alcohol-soluble portion of concretes, obtained by extracting the concretes with alcohol. Resinoids are perfume materials obtained by extraction of plant resinous substances with hydrocarbon solvents.

Tinctures are alcoholic solutions. In perfumery, these are generally the solutions obtained by maceration of various odorous materials with alcohol.

Natural products used in perfume include ambergris, benzoin, castoreum, civet, clove leaf oil, galbanum, jasmine absolute, labdanum, maté, melilot, mimosa, musk tonquin, myrrh, oakmoss or mousse de chêne, olibanum, opopanax, orris, patchouli, rosemary oil, sandalwood oil, vetivert oil, and violet leaves absolute.

Aroma Chemicals

During the last 20 years, there has been a rapid advance in the capabilities of instrumental techniques for the separation and identification of volatile organic substances. Of particular importance to the perfumery industry was the development of capillary gas chromatography columns and the ability to use them directly in tandem with a mass spectrometer. Computer technology is used to interpret the vast amount of data generated by such a combination of instruments. These developments along with Fourier transform nmr spectroscopy have allowed discovery and identification of extremely minute odoriferous samples and have revolutionized not only the analysis of essential oils and extractives but also the direction of the synthesis of aroma chemicals.

Research in aroma chemicals can be divided into three general categories: (*1*) duplication of naturally occurring chemicals, for example, phenethyl alcohol, which occurs in rose oil; (*2*) chemical modification of abundant, naturally occurring materials, eg, acetylated vetivert oil ("vetivert acetate") from vetivert oil, and vanillin (qv) from lignin (qv); and (*3*) synthesis based on industrial organic feedstocks, eg, nitro musks.

Aroma chemicals are usually cheap and available in any needed quantity (see also Alcohols, higher aliphatic; Aldehydes; Benzaldehyde; Benzoic acid; Cinnamic acid; Cinnamaldehyde; Cinnamyl alcohol; Coumarin; Esters, organic; Indole; Ketones; Salicyclic acid and related compounds; Terpenoids; Vanillin).

Odor Vocabulary

The descriptions and groups of fragrance raw materials are helpful in evaluating existing aroma chemicals or newly developed materials. To illustrate the use of the odor vocabulary, two well-known materials are

G

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dicyclohexylamine salt of trifluoroacetylglycylglycine: Weygand, Reiher, *Ber.* **88**, 26 (1955).

Crystals from dil alc. Crystal shape described as small tetrahedral leaves with a lustrous ball in center. Dec 262-264°. pK_1' 3.12; pK_2' 8.17. Heat of combustion: 472.4 kcal/mole. Soluble in hot water; slightly sol in ethanol: Practically insol in ether.

Hydrochloride, $C_4H_8N_2O_3.HCl.H_2O$, crystals from water + ethanol.

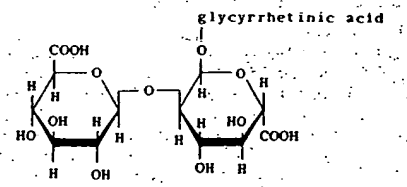
Ethyl ester hydrochloride, crystals from abs ethanol, dec 182°.

USE: In the synthesis of more complicated peptides.

4400. Glycyrrhiza. Licorice; liquorice; sweet root. Dried rhizome and roots of *Glycyrrhiza glabra* L., var. *typica* Regel & Herder (Spanish licorice), or of *G. glabra* L., var. *glandulifera* (Waldst. & Kit.) Regel & Herder (Russian licorice), or of other varieties of *G. glabra* yielding a yellow and sweet wood, *Leguminosae. Habit.* Southern Europe to Central Asia. *Constit.* 6-14% glycyrrhizin (the glucoside of glycyrrhetic acid), asparagine, sugars, resin. Used chiefly in the form of glycyrrhiza syrup. *Incompat.* Acids, metallic salts.

USE: Extract and syrup as pharmaceutic aids (flavor and flavored vehicles).

4401. Glycyrrhizic Acid. *20β-Carboxy-11-oxo-30-norolean-12-en-3β-yl-2-O-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid;* glycyrrhizin; glycyrrhizinic acid; glycyrrhetinic acid glycoside. $C_{42}H_{62}O_{16}$; mol wt 822.92. C 61.30%, H 7.59%, O 31.11%. Extraction from *Glycyrrhiza glabra* L.; *Leguminosae:* Karrer, Chao, *Helv. Chim. Acta* **4**, 100 (1921); Ruzicka, Louenberger, *ibid.* **19**, 1402 (1936). From commercial glycyrrhizinum ammoniacale: Tschirch, Cederberg, *Arch. Pharm.* **245**, 97 (1907); Voss *et al., Ber.* **70**, 122 (1937). Revised method of isoln: Conn, Conn, *J. Lab. Clin. Med.* **47**, 20 (1956). Structure: Lythgoe, Trippett, *J. Chem. Soc.* **1950**, 1983. Alternate view: Marsh, Levvy, *Biochem. J.* **63**, 9 (1956). *Review:* Nieman, *Chem. Weekbl.* **48**, 213 (1952). Synthesis of derivatives: Brieskorn, Sax, *Arch. Pharm.* **303**, 905 (1970).

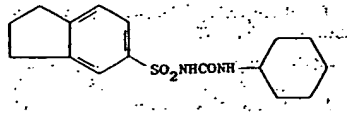


Crystals from glacial acetic acid. Intensely sweet taste. $[\alpha]_D^{17}$ +46.2° (c = 1.5 in alc). Freely sol in hot water, alcohol; practically insol in ether.

Ammonium glycyrrhizinate pentahydrate, $C_{42}H_{65}NO_{16}.5H_2O$, needles from 75% aqueous ethanol, decomp 212-217°. $[\alpha]_D^{20}$ +46.9° (c = 1.5 in 40% ethanol). uv max: 248 nm (ε 11,400). Sol in ammonia water, glacial acetic acid.

Dipotassium salt, $C_{42}H_{60}K_2O_{16}$, *Rizinsan K2 A2.*

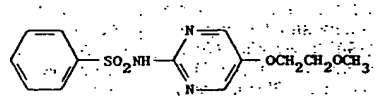
4402. Glyhexamide. *N-[(Cyclohexylamino)carbonyl]-2,3-dihydro-1H-indene-5-sulfonamide; 1-cyclohexyl-3-(5-indanylsulfonyl)urea;* 1-cyclohexyl-3-(5-hydrindenylsulfonyl)urea; SQ 15860; Subose. $C_{16}H_{22}N_2O_3S$; mol wt 322.45. C 59.60%, H 6.88%, N 8.69%, O 14.89%, S 9.95%. Prepd from hydrindene-5-sulfonamide and cyclohexyl isocyanate: Hoehn, Breuer, U.S. pat. 3,097,242 (1963 to Olin Mathieson). Clinical pharmacology: Grinnell *et al., Am. J. Med. Sci.* **253**, 312 (1967).



Crystals from 70% acetone, mp 153-155°.

THERAP CAT: Antidiabetic.

4403. Glymidine. *N-[5-(2-Methoxyethoxy)-2-pyrimidinyl]benzenesulfonamide;* 2-benzenesulfonamido-5-(β-methoxyethoxy)pyrimidine; glycodiazine. $C_{13}H_{15}N_3O_4S$; mol wt 309.35. C 50.47%, H 4.89%, N 13.58%, O 20.69%, S 10.37%. Prepn: Belg. pat. 609,270 corresp to H. Priewe *et al.*, U.S. pat. 3,275,635 (1962, 1966 to Schering, AG); Gutsche *et al., Arzneimittel-Forsch.* **14**, 373 (1964). Series of articles on pharmacology: *ibid.* 377-412. Activity: Losert *et al., ibid.* **23**, 1251 (1973). Metabolism: Soyfer *et al., Chim. Ther.* 5, 441 (1970).

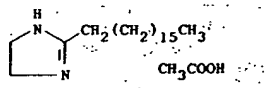


Crystals, mp 152-154°. Soly in ethanol: 0.91%; in toluene: 0.67%.

Sodium salt, $C_{13}H_{14}N_3NaO_4S$, *SH 717, Glyconormal, Gondafon, Lycanol, Redul.* Crystals, mp 221-226°. Sparingly sol in alc. Soly in water at 37°: 70.5%. LD_{50} in mice, rats (g/kg): 1.48, 2.00 i.v.; 5.30, 2.85 orally, Kramer *et al., Arzneimittel-Forsch.* **14**, 377 (1964).

THERAP CAT: Antidiabetic.

4404. Glyodin. *2-Heptadecyl-4,5-dihydro-1H-imidazole monoacetate;* 2-heptadecylglyoxalidine acetate; Crag Fungicide 341. $C_{22}H_{44}N_2O_2$; mol wt 368.59. C 71.68%, H 12.03%, N 7.60%, O 8.68%. Prepn from stearic acid and ethylenediamine: Kiff, U.S. pat. 2,540,171 (1951 to Union Carbide and Carbon).



Light orange crystals, mp 62-68°. d^{20} 1.035. Insol in water, acetone, toluene; sol in isopropanol. The base is a soft greasy wax, mp 94°.

USE: Fungicide.

4405. Glyoxal. *Ethanedial;* biformyl; diformyl; oxaldehyde. $C_2H_2O_2$; mol wt 58.04. C 41.39%, H 3.48%, O 55.14%. OHCCHO. Prepd by the oxidation of acetaldehyde by nitric or selenious acid: Lubawin, *Ber.* **8**, 768 (1875); Wyss, *Ber.* **10**, 1366 (1877); Kölln, *Ann.* **416**, 230 (1918); Riley *et al., J. Chem. Soc.* 1932, 1881; Ronzio, Waugh, *Org. Syn.* coll. vol. III, 438 (1955); by hydrolysis of dichlorodioxane: Butler, Cretcher, *J. Am. Chem. Soc.* **54**, 2988 (1932). Review of commercial development: J. F. Bohmfalk *et al., Ind. Eng. Chem.* **43**, 786 (1951). *Review:* A. B. Boese *et al.*, in *Glycols*, G. O. Curme, F. Johnston, Eds. (Reinhold, New York, 1952) pp 125-128.

Yellow prisms or irregular pieces turning white on cooling. d^{20} 1.14. Opaque at 10°, mp 15°, bp_{716} 51°. The vapor are green and burn with a purple flame. *Caution:* Mixtures with air may explode! $n_D^{20.5}$ 1.3826. Sol in anhydr solvents. pH of a 40% aq soln: 2.1-2.7; d_4^{20} 1.27. Polymerizes quickly on standing, on contact with water (violent reaction), or when dissolved in solvents contg water. The anhydr polymer changes to the monomer on heating. Solns of the monomer are obtained on heating the polymer with anethole, phenetole, safrole, methyl nonyl ketone, or benzaldehyde. LD_{50} orally in rats, guinea pigs: 2020, 760 mg/kg: Haag, Smyth *et al., J. Ind. Hyg. Toxicol.* **23**, 259 (1941).

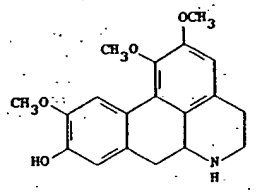
Dihydrate, $(OHCCHO)_3.2H_2O$, cryst powder, nonhygroscopic. More sol in hot water than in cold water. Commercially available in anhydr form as cryst dihydrate, or as 40% aq soln which may contain polymerization inhibitors.

Caution: Moderately irritating to skin, mucous membranes.

USE: In textiles, organic synthesis, glues, biocides.

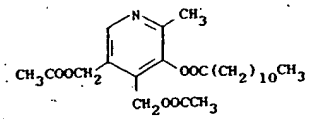
4406. Glyoxal-Sodium Bisulfite. *1,2-Dihydroxy-1,2-anedisulfonic acid disodium salt; glyoxal compound with sodium bisulfite.* $C_2H_4Na_2O_8S_2$; mol wt 266.16. C 9.02%, H 1.51%, Na 17.28%, O 48.09%, S 24.09%. Prepn: Kolb, Waugh, *Org. Syn.* coll. vol. III, 438 (1955).

5258. Laurotetanine. *5,6,6a,7-Tetrahydro-1,2,10-trimethoxy-4H-dibenzo[de,g]quinolin-9-ol; 1;2,10-trimethoxy-6aα-noraporphin-9-ol;* Litsoeine. $C_{19}H_{21}NO_4$; mol wt 327.37. C 69.70%, H 6.47%, N 4.28%, O 19.55%. From the bark of *Litsea citrata* Blume (*Tetranthera citrata* (Blume) Nees), *Lauraceae* and allied plants. Isoln: Greshoff, *Ber.* 23, 3537 (1890); Filippo, *Arch. Pharm.* 236, 601 (1898). Structure: Barger *et al., Ber.* 66, 450 (1933). Synthesis: Kikkawa, *C.A.* 53, 17163i (1959).



Monohydrate, needles, mp 125°. $[\alpha]_D^{25}$ +98.5°. Practically insol in water; freely sol in alcohol, chloroform, ethyl acetate, slightly in ether.

5259. 3-*O*-Lauroylpyridoxol Diacetate. *Dodecanoic acid 4,5-bis[(acetyloxy)methyl]-2-methyl-3-pyridinyl ester; lauric acid ester with pyridoxol diacetate (ester);* 5-lauroyloxy-6-methyl-3,4-pyridinedimethanol diacetate; 3-lauroyloxy-2-picoline-4,5-dimethanol diacetate; 2-methyl-3-lauroyloxy-4,5-diacetoxymethylpyridine; Epixine; Rosamit. $C_{24}H_{37}NO_6$; mol wt 435.54. C 66.18%, H 8.56%, N 3.22%, O 22.04%. Prepn: Belg. pat. 640,827 (1964 to Soc. Belge Azote Prod. Chim. Marly), *C.A.* 63, 587h (1965).



Crystals, mp 44°. Practically insol in water; sol in ether, chloroform, ethanol, ethylene dichloride.

THERAP CAT: Antiseborrheic.

5260. Lauryl Bromide. *1-Bromododecane;* dodecyl bromide. $C_{12}H_{25}Br$; mol wt 249.24. C 57.82%, H 10.11%, Br 32.06%. $CH_3(CH_2)_{10}CH_2Br$. Prepd by the action of hydrobromic acid on primary *n*-lauryl alcohol in the presence of sulfuric acid: Kamm, Marvel, *Org. Syn.* 1, 7 (1921).

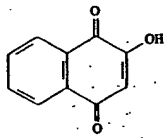
Liquid. bp_{45} 175-180°. Insol in water. Sol in alc, ether.

5261. Lavender. Garden lavender; true lavender. Flowers of *Lavandula officinalis* Chaix (*L. vera* DC.), *Labiatae. Habit.* Mediterranean region. *Constit.* Volatile oil.

USE: For fumigating; in perfumery; to keep moths from clothes; manuf oil lavender. Pharmaceutic aid (perfume).

5262. Lawrencium. Lr; formerly Lw; at. wt (longest-lived known isotope, $T_{1/2}$ ~ 3 minutes) 260; at. no. 103; valence 3. Known isotopes 255-260. Discovery of first isotope claimed by Ghiorso *et al., Phys. Rev. Letters* 6, 473 (1961). Prepared by bombardment of californium with boron ions; originally assigned mass number 257; later changed to 258 ($T_{1/2}$ 4.2 seconds, α-emitter): Eskola *et al., Phys. Rev. C* 4, 632 (1971). Prepn of ^{256}Lr ($T_{1/2}$ ~ 45 seconds) by irradiating ^{243}Am with ^{18}O ions: Donets *et al., At. Energ. (USSR)* 19, 109 (1965), *C.A.* 64, 1542c (1966). Prepn of isotopes 255-260 by bombardment of transuranium elements with heavy ions: Eskola *et al., loc. cit.* Reviews of history, prepn and properties: C. Keller, *The Chemistry of the Transuranium Elements* (Verlag Chemie, Weinheim, English Ed., 1971) pp 609-612; Silva, "Trans-Curium Elements" in *MFP Int. Rev. Sci.: Inorg. Chem., Ser. One* vol. 8, A. G. Maddock, Ed. (University Park Press, Baltimore, 1972) pp 71-105; Ghiorso, *Handb. Exp. Pharmakol.* 36, 691-715 (1973); Taylor, *ibid.* 717-738.

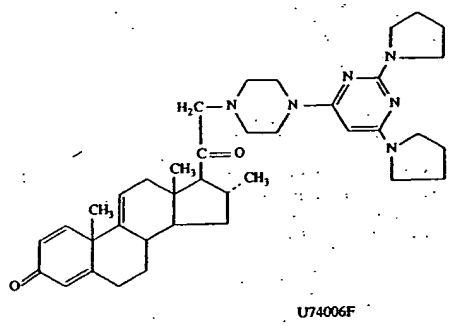
5263. Lawsone. *2-Hydroxy-1,4-naphthalenedione; 2-hydroxy-1,4-naphthoquinone.* $C_{10}H_6O_3$; mol wt 174.15. C 68.96%, H 3.47%, O 27.56%. From leaves of *Lawsonia inermis* L. and *L. alba* Lam., *Lythraceae:* Latif, *Indian J. Ag. Sci.* 29, No. 2-3, 147 (1959), *C.A.* 55, 14828g (1961). Synthesis: Fieser, *J. Am. Chem. Soc.* 70, 3165 (1948); Jam. Seshadri, *Proc. Indian Acad. Sci.* 35A, 233 (1952); Eistert, Müller, *Ber.* 92, 2071 (1959).



Yellow prisms from acetic acid, dec 195-196°.

THERAP CAT: Ultraviolet screen.

5264. Lazaroids. Novel class of nonglucocorticoid 21-aminosteroid antioxidants which inhibit lipid peroxidation. A representative compound is known as *U74006F.* Prepn: J. M. McCall *et al.,* PCT Int. pat. Appl. 87 01,70[illegible] (1987 to Upjohn), *C.A.* 108, 6287u (1987). Inhibition of iron-dependent lipid peroxidation *in vitro:* J. M. Braughler *et al., J. Biol. Chem.* 262, 10438 (1987). Endocrinological profile in mice: J. M. Braughler *et al., J. Pharmacol. Exp. Ther.* 244, 423 (1988). HPLC determn in plasma: J. W. Cox, R. H. Pullen, *J. Chromatog.* 424, 293 (1988). *In vivo* attenuation of vasogenic brain edema: E. D. Hall, M. A. Travis, *Brain Res.* 451, 350 (1988). Effects on experimental head injury in mice: E. D. Hall *et al., J. Neurosurg.* 68, 45[illegible] (1988); in post-traumatic spinal cord ischemia in cats: E. D. Hall, *ibid.* 462. Review of development and potential clinical applications in trauma and stroke: J. M. McCall *et al., Acta Anaesthesiol. Belg.* 38, 417-420 (1987).



U74006F

U74006F, $C_{39}H_{56}N_6O_5S$, *21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione monomethanesulfonate.* Monohydrate, mp 181-185° (dec). uv max: 234, 285 nm (ε 52000, 17000).

5265. Lazurite. Lapis lazuli; lasurite. Composition $(Na,Ca)_4(AlSiO_4)_3(SO_4,S,Cl)$, E. S. Dana, *A System of Mineralogy* (John Wiley, New York, 6th ed., 1901) pp 432-433; S. Hurlbut, Jr., *Dana's Manual of Mineralogy* (John Wiley, New York, 17th ed., 1959) p 503.

Blue, blue-violet or greenish-blue, translucent, cubic, dodecahedral crystals. d 2.4. Dec by HCl with pptn of S and evolution of H_2S.

USE: In manuf of vases, ornamental furniture, mosaics, paints, jewelry.

5266. LBF. Lactobacillus bulgaricus factor. Growth factor occurring in products derived from both animal and plant sources and in culture filtrate of certain microorganisms: Williams *et al., J. Biol. Chem.* 177, 933 (1949); Vitamins *et al., Arch. Biochem. Biophys.* 34, 409 (1951); Peters *et al., Am. Chem. Soc.* 75, 1688 (1953). Contains pantetheine which is oxidized during purification to the disulfide, pantethine *q.v.* Natural occurrence of several different forms. LBF each being a mixed disulfide of pantetheine: Rasmussen *et al., Proc. Soc. Exp. Biol. Med.* 73, 658 (1950); Brown, Snell, *J. Biol. Chem.* 198, 375 (1952). Coenzyme A digest with intestinal phosphatase shows 2-4 LBF-active components: Long, Williams, *J. Bacteriol.* 61, 195 (1951). *Ref.*

Remington's Pharmaceutical Sciences

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Milk chocolate is a mixture of sweet chocolate and milk powder or other dairy product. Chocolate and the products described above contain the purines theobromine and caffeine, and considerable quantities of fat (cocoa butter or theobroma oil), as well as protein and starch. These factors are lowered in sweet chocolate because of the large amount of added sugar (more than 50% of the final product).

Description—Weak reddish to purplish brown to moderate brown powder having a chocolate-like odor and taste, free from sweetness.

Uses—A food and pharmaceutically as a flavor in tablets, syrups, pill and tablet coatings, troches, etc.

Cocoa Syrup—page 1301.

Coriander—page 1299.

Coriander Oil

The volatile oil distilled with steam from the dried ripe fruit of *Coriandrum sativum* Linné (Fam *Umbelliferae*).

Constituents—The alcohol *d-linaloôl* (formerly termed *"coriandrol"*) is the chief constituent of this oil, occurring in amounts varying from 60 to 80%. Other constituents include *l-borneol, geraniol, pinenes, terpinenes* and *p-cymene.*

Description—Colorless or pale yellow liquid, having the characteristic odor and taste of coriander; specific gravity 0.863 to 0.875.

Solubility—Soluble in 3 volumes of 70% alcohol.

Uses—A flavoring agent. It formerly was employed in a dose of 0.1 mL as a *carminative.*

Denatonium Benzoate—page 1321.

Eriodictyon

Consumptives' Weed; Mountain Balm; Yerba Santa

The dried leaf of *Eriodictyon californicum* (Hooker et Arnott) Torrey (Fam *Hydrophyllaceae*).

Constituents—A bitter *resin, volatile oil, eriodictyonone* [$C_{16}H_{14}O_6$, also called *homoeriodictyol*], *fixed oil, tannin, gum,* etc.

Uses—A pharmaceutical necessity. It is used in the preparation of *Eriodictyon Fluidextract.*

Eriodictyon Fluidextract [Yerba Santa Fluidextract]—*Preparation:* Using Eriodictyon (in moderately coarse powder, 1000 g), prepare the fluidextract by Process A (page 1543), using a mixture of 4 volumes of alcohol and 1 volume of water as the menstruum. Macerate the drug during 48 hr, then percolate at a moderate rate and reserve the first 800 mL of percolate. *Alcohol Content:* 57 to 62%. *Uses:* A peculiar, aromatic *flavor* used in syrups and elixirs, especially for masking the taste of bitter drugs like quinine. Because of its resinous character it requires an alkali to render it soluble in aqueous mixtures.

Eriodictyon Syrup, Aromatic—page 1301.

Ethyl Acetate

Acetic acid, ethyl ester; Acetic Ether

$CH_3COOC_2H_5$

Ethyl acetate [141-78-6] $C_4H_8O_2$ (88.11).

Preparation—By slow distillation of a mixture of alcohol and acetic acid in the presence of sulfuric acid.

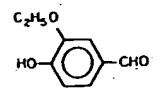
Description—Transparent, colorless liquid with a fragrant and refreshing, slightly acetous odor, and a peculiar acetous, burning taste; specific gravity 0.894 to 0.898; distils 76 to 77.5°.

Solubility—1 mL in about 10 mL of water; miscible with alcohol, acetone, ether, chloroform or fixed and volatile oils.

Uses—Chiefly as a *flavoring agent.* It is used industrially in artificial fruit essence, as a *solvent* for nitrocellulose varnishes and lacquers and as a solvent in organic chemistry.

Ethyl Vanillin

Benzaldehyde, 3-ethoxy-4-hydroxy-, Bourbanal; Ethovan; Vanillal; Vanirome



3-Ethoxy-4-hydroxybenzaldehyde [121-32-4] $C_9H_{10}O_3$ (166.18).

Preparation—By reacting *o*-ethoxyphenol with formaldehyde and *p*-nitrosodimethylaniline in the presence of aluminum and water.

Description—Fine, white or slightly yellowish crystals; odor and taste similar to vanillin; affected by light; solutions are acid to litmus; melts about 77°.

Solubility—1 g in about 100 mL of water at 50°; freely soluble in alcohol, chloroform, ether or solutions of fixed alkali hydroxides.

Uses—A *flavor,* like vanillin, but stronger.

Eucalyptus Oil

The volatile oil distilled with steam from the fresh leaf of *Eucalyptus globulus* Labillardière or of some other species of *Eucalyptus* L'Heritier (Fam *Myrtaceae*). It contains not less than 70% of $C_{10}H_{18}O$ (eucalyptol).

Constituents—The most important constituent is *eucalyptol* (*cineol*). Other compounds include *d-a-pinene, globulol, pinocarveol, pinocarvone* and several aldehydes.

Description—Colorless or pale yellow liquid, having a characteristic, aromatic, somewhat camphoraceous odor, and a pungent, spicy, cooling taste; specific gravity 0.905 to 0.925 at 25°.

Solubility—Soluble in 5 volumes of 70% alcohol.

Uses—A *flavoring agent* and an *expectorant* in chronic bronchitis. It also has *bacteriostatic* properties. This oil may be toxic.

Fennel Oil

The volatile oil distilled with steam from the dried ripe fruit of *Foeniculum vulgare* Miller (Fam *Umbelliferae*).

Note—If solid material has separated, carefully warm the oil until it is completely liquefied, and mix it before using.

Constituents—*Anethole* [$C_{10}H_{12}O$] is the chief constituent, occurring to the extent of 50 to 60%. Some of the other constituents are *d*-pinene, phellandrene, dipentene, fenchone, methylchavicol, anisaldehyde and anisic acid.

Description—Colorless or pale yellow liquid, having the characteristic odor and taste of fennel; specific gravity 0.953 to 0.973; congealing temperature is not below 3°.

Solubility—Soluble in 8 volumes of 80% alcohol or in 1 volume of 90% alcohol.

Uses—A flavoring agent. It formerly was employed in a dose of 0.1 mL as a *carminative.*

Glycyrrhiza

Licorice Root; Liquorice Root; Sweetwood; Italian Juice Root; Spanish Juice Root

The dried rhizome and roots of *Glycyrrhiza glabra* Linné, known in commerce as Spanish Licorice, or of *Glycyrrhiza glabra* Linné var *glandulifera* Waldstein et Kitaibel, known in commerce as Russian Licorice, or of other varieties of *Glycyrrhiza glabra* Linné, yielding a yellow and sweet wood (Fam. *Leguminosae*).

Constituents—This well-known root contains 5 to 7% of the sweet principle *glycyrrhizin,* or *glycyrrhizic acid* which is 50 times as sweet as cane sugar. There also is present an oleoresinous substance to which its slight acridity is due. If alcohol or an alkali is used as a menstruum for the root and the preparation not treated to deprive it of acridity, it will have a disagreeable aftertaste. For this reason boiling water is used for its extraction in both the extract and the fluidextract.

Description—The USP/NF provides descriptions of *Unground Spanish and Russian Glycyrrhizas, Histology* and *Powdered Glycyrrhiza.*

Uses—Valuable in pharmacy chiefly for its *sweet flavor.* It is one of the most efficient substances known for masking the taste of bitter substances, like quinine. Acids precipitate the glycyrrhizin and should not be added to mixtures in which glycyrrhiza is intended to mask disagreeable taste. Most of the imported licorice is used

black color externally, and a brittle, sharp, smooth, conchoidal fracture; the extract has a characteristic and sweet taste which is not more than very slightly acrid. *Uses:* A *flavoring agent.*

Lavender [Lavandula]—The flowers of *Lavandula spica* (*Lavandula officinalis* or *Lavandula vera*); contains a volatile oil with the principal constituent *l*-linalyl acetate. *Uses:* A *perfume.*

Lemon Peel USP XV, BP [Fresh Lemon Peel]—The outer yellow rind of the fresh ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*); contains a volatile oil and hesperidin. *Uses:* A *flavor.*

Lemon Tincture USP XVIII [Lemon Peel Tincture]—*Preparation:* From lemon peel, which is the outer yellow rind of the fresh, ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*), by *Process M* (page 1543), 500 g of the peel being macerated in 900 mL alcohol and the preparation being completed with alcohol to make the product measure 1000 mL. Use talc as the filtering medium. The white portion of the rind must not be used, as the proportion of oil, which is found only in the yellow rind, is reduced and the bitter principle, hesperidin, introduced. *Alcohol Content:* 62 to 72%. *Uses:* A flavor, its fineness of flavor being assured as it comes from the fresh fruit, and being an alcoholic solution it is more stable than the oil.

Myrcia Oil [Bay Oil; Oil of Bay]—The volatile oil distilled from leaves of *Pimenta racemosa* (Miller) J W Moore (Fam *Myrtaceae*); contains the phenolic compounds eugenol and chavicol. *Uses:* In the preparation of bay rum as a *perfume.*

Orange Oil, Bitter—The volatile oil obtained by expression from the fresh peel of the fruit of *Citrus aurantium* Linné (Fam *Rutaceae*); contains primarily *d*-limonene. Pale yellow liquid with a characteristic, aromatic odor of the Seville orange; if it has a terebinthinate odor, it should not be dispensed; refractive index 1.4725 to 1.4755 at 20°. It differs little from *Orange Oil* (page 1296) except for the botanical source. Miscible with anhydrous alcohol and with about 4 volumes alcohol. *Uses:* A *flavor.*

Orange Peel, Bitter [Bitter Orange; Curacao Orange Peel; Bigarade Orange]—The dried rind of the unripe but fully grown fruit of *Citrus aurantium* Linné (Fam *Rutaceae*). *Constituents:* The inner part of the peel from the bitter orange contains a volatile oil and the glycoside *hesperidin* ($C_{28}H_{34}O_{15}$). This, upon hydrolysis in the presence of H_2SO_4, yields *hesperetin* ($C_{16}H_{14}O_6$), *rhamnose* ($C_6H_{12}O_5$), and D-glucose ($C_6H_{12}O_6$). *Uses:* A *flavoring agent.* It has been used as a bitter.

Orange Peel, Sweet USP XV—The fresh, outer rind of the non-artificially colored, ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*); the white, inner portion of the rind is to be excluded. Contains a volatile oil but no hesperidin, since the glycoside occurs in the white portion of the rind. *Uses:* A *flavor.*

Orris [Orris Root; Iris; Florentine Orris]—The peeled and dried rhizome of *Iris germanica* Linné, including its variety *florentina* Dykes (*Iris florentina* Linné), or of *Iris pallida* Lamarck (Fam *Iridaceae*); contains about 0.1 to 0.2% of a volatile oil (orris butter), myristic acid and the ketone irone; irone provides the fragrant odor of orris. *Uses:* A *perfume.*

Pimenta Oil [Pimento Oil; Allspice Oil]—The volatile oil distilled from the fruit of *Pimenta officinalis* Lindley (Fam *Myrtaceae*). *Uses:* A *carminative* and *stimulant* and also as a *condiment* in foods.

Rosemary Oil—The volatile oil distilled with steam from the fresh flowering tops of *Rosmarinus officinalis* Linné (Fam *Labiatae*); yields not less than 1.5% of esters calculated as bornyl acetate ($C_{12}H_{20}O_2$), and not less than 8% of total borneol ($C_{10}H_{18}O$), free and as esters. *Constituents:* The amount of esters, calculated as bornyl acetate, and of total borneol, respectively, varies somewhat with its geographic source. Cineol is present to the extent of about 19–25%, depending on the source. The terpenes *d*- and *l*-*α*-*pinene*, *dipentene* and *camphene*, and the ketone *camphor* also occur in this oil. *Description:* Colorless or pale yellow liquid, having the characteristic odor of rosemary, and a warm, camphoraceous taste; specific gravity 0.894 to 0.912. Soluble in 1 volume of 90% alcohol, by volume, but upon further dilution may become turbid. *Uses:* A *flavor* and *perfume*, chiefly, in rubefacient liniments such as *Camphor and Soap Liniment.*

Sassafras—The dried bark of the root of *Sassafras albidum* (Nuttall) Nees (Fam *Lauraceae*). *Uses:* Principally because of its high content of volatile oil which serves to disguise the taste of disagreeable substances. An infusion (*sassafras tea*) formerly was used extensively as a home remedy, particularly in the southern states.

Sassafras Oil—The volatile oil distilled with steam from *Sassafras.* *Uses:* A *flavor* by confectioners, particularly in hard candies. Either the oil or safrol is used as a *preservative* in mucilage and library paste, being far superior to methyl salicylate for this purpose. Since the oil is *antiseptic*, it sometimes is employed in conjunction with other agents for local application in diseases of the nose and throat; safrol also is used in this way.

Wild Cherry [Wild Black Cherry Bark]—The carefully dried stem bark of *Prunus serotina* Ehrhart (Fam *Rosaceae*), free of borke and preferably having been collected in autumn. *Constituents:* A glucoside of *d*-*mandelonitrile* ($C_6H_5.CHOH.CN$) known as *prunasin* (page 385), the enzyme *emulsin*, tannin, a bitter principle, starch, resin, etc. In the BP and the English literature this drug has been termed "Virginian Prune"—a literal but incorrect translation of the older botanical name, *Prunus virginiana.* *Uses:* A *flavoring agent*, especially in cough preparations. It is an ingredient in *Wild Cherry Syrup.* As with bitter almond, contact with water, in the presence of emulsin, results in the production of benzaldehyde and HCN. All preparations of wild cherry should be made without heat in order to avoid destruction of the enzyme which is responsible for the production of the free active principles.

Diluting Agents

Diluting agents (vehicles or carriers) are indifferent substances which are used as solvents for active medicinals. They are of primary importance for diluting and flavoring drugs which are intended for oral administration, but a few such agents are designed specifically for diluting parenteral injections. The latter group is considered separately.

The expert selection of diluting agents has been an important factor in popularizing the "specialties" of manufacturing pharmacists. Since a large selection of diluting agents is available in a choice of colors and flavors, the prescriber has an opportunity to make his own prescriptions more acceptable to the patient. The best diluting agent is usually the best solvent for the drug. Water-soluble substances, for example, should be flavored and diluted with an aqueous agent and alcohol-soluble drugs with an alcoholic vehicle. Thus, the diluting agents presented herein are divided into three groups on the basis of their physical properties: aqueous, hydroalcoholic and alcoholic.

Aqueous Diluting Agents

Aqueous diluting agents include aromatic waters, syrups and mucilages. Aromatic waters are used as diluting agents for water-soluble substances and salts, but cannot mask the taste of very disagreeable drugs. Some of the more common flavored aqueous agents and the official forms of water are listed below.

Orange Flower Water

Stronger Orange Flower Water; Triple Orange Flower Water

A saturated solution of the odoriferous principles of the flowers of *Citrus aurantium* Linné (Fam. *Rutaceae*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

Description—Should be nearly colorless, clear or only faintly opalescent; the odor should be that of the orange blossoms; it must be free from empyreuma, mustiness and fungoid growths.

Uses—A *vehicle flavor* and *perfume* in syrups, elixirs and solutions.

Peppermint Water

A clear, saturated solution of peppermint oil in purified water, prepared by one of the processes described under *Aromatic Waters* (page 1522).

Uses—A *carminative* and *flavored vehicle.*

Dose—15 mL.

Tolu Balsam Syrup—page 1299.

Water

Water [7732-18-5] H_2O (18.02).

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Hirsch

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[54] **USE OF ODORANTS TO TREAT MALE IMPOTENCE, AND ARTICLE OF MANUFACTURE THEREFOR**

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[58] **Field of Search** 424/451, 489, 424/58, 45, 46, 434

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[57] **ABSTRACT**

A method is provided for inducing or enhancing penile erection through the delivery of odorants for inhalation. The administration of odorants provides an increase in blood flow to the penis, and a therapeutic aid to stimulate sexual activity and alleviate male vasculogenic impotence.

23 Claims, No Drawings

USE OF ODORANTS TO TREAT MALE IMPOTENCE, AND ARTICLE OF MANUFACTURE THEREFOR

BACKGROUND OF THE INVENTION

In men, the genital component of the excitement phase of the sexual response cycle is manifested by penile erection and scrotal elevation (Kolodny, Masters and Johnson, *Textbook of Sexual Medicine*, pages 507–508, Little, Brown and Company, Boston, Mass. (1979)). Erection is basically a cardiovascular event that is controlled by the nervous system. The first physical sign of sexual excitation is a change in penile blood flow. Blood flow increases to the penis with sexual excitement and is reduced with sexual inhibition.

Male erectile dysfunction, or impotence, is the inability to achieve or sustain an erection of sufficient rigidity to have sexual intercourse. The causes of impotence are psychological and/or organic (i.e., endocrinologic, neurogenic and vasculogenic). Ten to fifteen percent of male impotence is organic in nature. Organic causes can be from local lesions of the genitalia, endocrine diseases, organic lesions of the nervous system, and/or vasculogenic impotence from reduced blood flow is the most common organic cause usually seen in diabetes. Impotence may be a side effect of a therapeutic drug or associated with a disease such as multiple sclerosis, diabetes and sickle cell anemia, and can be exacerbated by smoking, inadequate diet among other factors. Emotional disturbances, including stress, fatigue or distraction, can also cause impotence.

In the sexual response, neuromuscular events simultaneously increase the amount of blood entering the organ and decrease the rate at which blood is allowed to leave it. Three vascular changes have been indicated in causing erection: shunting of blood into the cavernous spaces, contraction of muscular polsters on deep efferent veins, and vasoconstriction-induced reduction in superficial penile blood flow (G. Conti, *Octa. Anat.* 14:17 (1952)). As a function of the autonomic nervous system, penile engorgement is controlled by arterial flow through the pudendal artery and the smaller arteries to the penis. The increased arterial flow is accomplished by active dilatation of the arterioles. The process is reversed by the sudden constriction of the arterioles that accompanies ejaculation.

Alteration of blood flow to and from the penis is considered to be the most frequent organic cause of impotence. Vasculogenic impotence results from either arterial occlusion, i.e., the obstruction of adequate blood flow to the penile arteries, or excess venal outflow (cavernovenous leaking).

Treatment of impotence can include counseling directed toward dealing with the male's insecurities and feelings to reduce fears of sexual performance. Treatments for male impotence include surgery, penile prostheses implants including flexible rods and inflatable balloons, drugs such as vasodilators given to induce an erection as an ointment for topical application or a solution for transurethral injection, and external aids such as penile splints to support the penis or constricting rings to alter the blood flow through the penis. A drawback of those systems is their invasiveness, unwanted side effects, cost, inconvenience, and complexity.

Accordingly, an object of the invention is to provide a method of stimulating the male sexual response and inducing penile erection, that is non-invasive and easy to perform. Another object is to induce normal male sexual arousal.

SUMMARY OF THE INVENTION

These and other objects are achieved by the present invention which is directed to a method for stimulating the male sexual response through the delivery of an odorant substance for inhalation. The use of the odorants is particularly useful as adjuvants for inducing or enhancing an erection, and as aids for a non-invasive treatment of male vasculogenic impotence.

It was found that the administration of odorants for inhalation by a male individual having a normal olfactory ability effectively increased penile blood flow from about 2–40%, and enhanced sexual arousal. Preferred odorants are those that provided a 20–40% increase in blood flow to the penis, which includes lavender, oriental spice, cola and orange, and odorant mixtures of lavender and pumpkin pie, doughnut and black licorice, and pumpkin pie and doughnut. The odorants are useful as adjuvants to augment penile blood flow and as aids in the treatment of male impotence, and to enhance sexual arousal in normal males, i.e., those without sexual dysfunction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a non-invasive method of increasing blood flow to the penis to augment penile erection, and of treating vasculogenic impotence through the use of odorants. The method is particularly useful for males who have a normal olfactory ability. Administration of the odorant to a male subject will increase penile blood flow such that in a normosmic person for which the odor is hedonically positive, the blood flow will increase by about 2–40% compared to blood flow without being given the odorant. Preferably, the odorant induces or enhances an erection sufficient for vaginal penetration.

Preferably, an odorant is administered that will increase penile blood flow by about 2–60%, preferably about 15–50%. Preferred odorants are those that increase blood flow by about 20–40%, which include, for example, lavender, oriental spice, cola and orange odorants, and odorant mixtures such as lavender and pumpkin pie, doughnut and black licorice, pumpkin pie and doughnut, and lavender and doughnut. Odorants useful in the present method are commercially available, for example, from International Flavors and Fragrances, Inc. (IFF), New York, N.Y.

The precise magnitude of a loss of smell may be determined by means of an odor threshold test. According to that test, an odorant substance such as butyl alcohol, phenyl ethyl alcohol or pyridine, is combined in an odorless liquid medium to provide a series of dilutions, or binary steps, of the odorant. For each successive binary step up the dilution scale, the odorant is present, for example, at one half the concentration of the preceding step. The highest concentration of the odorant usually provides the substance at an irritant level. The patient is presented with the series of dilutions in ascending order, and is asked to compare each dilution step to at least one control stimulus, such as odorless propylene glycol.

A "normosmic" individual is able to detect the odor of an odorant substance without irritant sensations when the substance is presented at a concentration within a range of the average normal threshold for the substance. A "hyposmic" individual is one who has a reduced capacity of the olfactory nerve being able to detect an odorant substance by its odor at a concentration, or decismel level, above that of a normosmic individual yet below its irritant concentration level. An "anosmic" individual is one who has essentially no olfactory nerve capacity being unable to detect the odor of the odorant substance, but has trigeminal nerve function, being able to detect an odorant substance by means of

irritant, tingling sensations when it is present at an irritant concentration. A patient who is able to detect pyridine vapor by means of irritant, tingling sensations caused by stimulation of the trigeminal nerve, but who cannot distinguish a pyridine odor at a lower concentration without such sensation, is considered to be anosmic having no olfactory nerve sensitivity. The term "microsmic" is synonymous with hyposmic.

The only limitation on the character of the odorant that is used is that it must be suprathreshold in intensity and not trigeminal in nature. According to the method of the invention, an odorant and/or odorant mixture is administered to a male subject/patient for sniffing and inhalation into the nasal passageway, to deliver an amount of the odorant effective to increase penile blood flow which is a suprathreshold level but not irritative in nature.

An odorant is presented at a suprathreshold level when the decismel level or concentration of the odorant is high enough to be detected by a normosmic individual. At its irritative level, the odorant level or concentration is so high that the odorant stimulates predominantly the trigeminal nerve rather than the olfactory nerve and, hence, is perceived as noxious. The irritation threshold of the patient is the lowest concentration of the substance that causes immediate stinging or burning sensations in the nose, or stinging or lacrimation of the eye. (See, J. F. Gent, in *Clinical Measurement of Taste and Smell*, pages 107–166, H. L. Meiselman et al. (eds). 602 pp., MacMillan, NY (1986); R. L. Doty et al., *Ann. Neurol.* 25: 166–171 (1989); E. Koss et al., *Neurology* 38: 1228–1232 (1988); R. Doty, *The Smell Identification Test: Administration Manual* 1983: 13–14, Philadelphia: Sensonics, Inc. (1983)).

The effect of the odorant and/or odorant mixture can be assessed objectively by administering a test to the subject to measure initial penile blood flow, and then re-testing the blood flow after being given the odorant. The effectiveness of the odorant on the subject can be observed by comparing the amount of penile blood flow before and after inhaling the odorant.

The use of the odorant or odorant/mixture is useful for increasing penile blood flow in a male individual who does or does not suffer from vasculogenic impotence to improve penile erection. Male vasculogenic impotence is the result of primary small vessel disease or is a secondary symptom of a disease such as diabetes, atherosclerosis or amyloidosis, for example.

The odorant can be delivered to the subject in the form of a liquid solution, aerosol spray, solid, microcapsules, or other suitable form to deliver an amount of the odorant for sniffing by the person to increase blood flow to the penis and effectuate and/or enhance penile erection and sexual arousal. A preferred amount of the odorant that is delivered is a suprathreshold but not irritative level.

The odorant substance can be administered in combination with an odorless liquid carrier such as mineral oil or water, and can be formulated with a viscosity effective to allow for aerosolization. The odorant can be dispensed, for example, by means of a cloth material that is coated with the odorant, as a solid or liquid form contained in a capped vessel, as a spray from an aerosol or pump-type spray device, as a nasal spray, by opening a blister pack or scratch-and-sniff odor patch containing the odorant in the form of microspheres, a vaporous emission from a pen-like dispenser containing a liquid form of the odorant adsorbed to a wicking material, a vapor from a solid or liquid air freshener, a lotion or cream, perfume or cologne, potpourri, incense, a lightbulb ring or candle, and the like. The odorant can be provided in a portable dispenser for ready individual and personal use, for example, by means of a pen-like delivery device, a blister pack, a small vial of lotion, a booklet of scratch-and-sniff odor patches, and the like, that include an effective amount of the desired odorant substance.

The odorant substance or odorant mixture can be packaged as a part of an article of manufacture, or kit, for use in increasing penile blood flow and/or enhancing penile erection. The kit can include in association, for example, an effective amount of an odorant and/or odorant mixture in a non-reactive, biocompatible carrier and/or optional additives as desired such as an antioxidant, preservative, and the like; and means for containing the odorant such as a vial, jar, pouch, can, bottle, cloth, aerosol can, blister pack, scratch-and-sniff odor patch, pen-like device, and the like. The containing means can include means for spraying by aerosolization or pumping. The kit can further include means for instructing the user about the use of the odorant and/or mixture to stimulate penile blood flow, in the form of a label or tag attached to the packaging and/or a printed package insert. The parts of the kit can be contained or separately packaged within a packaging material, such as a box or bag.

The invention will be further described by reference to the following detailed examples, wherein the methodologies are as described below. These examples are not meant to limit the scope of the invention that has been set forth in the foregoing description. Variation within the concepts of the invention are apparent to those skilled in the art. The disclosures of the cited references are incorporated by reference herein.

EXAMPLE

A randomized double-blind study was conducted to assess the effect of odorants on penile blood flow, a measure of the level of male excitation. Thirty-one men underwent penile blood flow measurements with a bi-directional doppler ultrasound while wearing masks with a total of 46 different odors and 2 control masks. All subjects underwent standardized smell tests. The brachial/penile index (BPI) with blank masks (as baseline) was compared with each odorized mask for each individual as well as for the group as a whole. Data was analyzed using the Wilcoxan Rank Sum Test and Spearman's Rank Correlation Coefficients.

The odors with the greatest increase in BPI were a mixture of lavender and pumpkin pie, doughnut and black licorice, and pumpkin pie and doughnut. In subjects with normal olfactory ability and whose partners wear cologne, lavender had the greatest impact on BPI ($p=0.03$). The ability for oriental spice ($p=0.01$), cola ($p=0.02$) and lavender ($p=0.02$) to increase BPI positively correlated with the number of times the subject had intercourse in the last month. The results showed that, in those men with a normal olfactory ability, a variety of odors can increase penile blood flow.

Testing Procedure. Thirty-one male volunteers from 18–64 years of age (mean 30.2) underwent olfactory testing with the University of Pennsylvania Smell Identification Test (UPSIT), a 40-question forced-choice, scratch-and-sniff identification test and the Chicago Smell Test, a 3-item detection and identification test (Doty et al., *Chemical Senses* 10:297–300 (1985); Hirsch et al., *Chemical Senses* 17:642–643 (1992); Hirsch et al., *Chemical Senses* 18 (5):570–571 (1993); Hirsch et al., *Chemical Senses* 18 (5):571 (1993)).

Each male subject was also queried as to sexual preferences, sexual practices, and odor hedonics. Questions

asked were as follows: age; marital status (s; m; w; d); height and weight; whether an odor made him recall his childhood and, if yes, what odor; if he wears a cologne and, if yes, what cologne; if he has diabetes; if he had any difficulty with obtaining an erection in the last 30 days and, if yes, the approximate number of times; if he smokes and, if yes, the number of cigarettes daily; favorite food (specific); least favorite food (specific); approximate number of times he had sexual intercourse in the last 30 days; approximate number of sexual partners in the last 30 days; sexual preference (male; female); how satisfied with his current sexual activity on a rating scale of 1-2-3-4-5, where 1=very unsatisfied and 5=satisfied; number of times he had an erection upon awakening within the last 30 days on a scale of 1-2-3-4-5, where 1=never, 3=sometimes, 5=always; and if there was a particular odor to cause him to have an erection within the last 30 days (yes, no) and, if yes, what odor.

Subjects underwent assessment of level of sexual arousal as determined by the brachial penile index (Laws et al., "The Penile Plethysmograph," in A Practioner's Guide to Treating the Incarcerated Male Sex Offender, pages 85–93, B. K. Schwartz and H. R. Cellini (eds.), U.S. Department of Justice, National Institute of Corrections, Washington D.C. (1988)). The test was performed with the FLOSCOPE ULTRA Pneumoplethysmograph following manufacturer's protocol (LifeSigns Corporation, "The PC Compatible FLOSCOPE ULTRA Vascular Lab", Minneapolis, Minn. (1994)). With this instrument, both penile and brachial blood pressures were measured and their ratio calculated, thus controlling for systemic effects. This allowed specific non-invasive assessment of penile blood flow.

All subjects underwent assessments as follows. After being attached to the plethysmograph, 3 minutes were allowed for acclamation to the experimental environment. Following this, a blank control mask was applied for 1 minute and then brachial penile index was recorded. The masks were made of 3-M paper surgical masks, and were designed to cover the nose and mouth. The mask was removed and then the 46 odorized masks were randomly presented in a double-blinded fashion. The odorized masks were prepared by applying about 1 drop of odorant to provide a non-irritant but suprathreshold level of the scent (i.e., a level wherein the subject could detect the odor was present, but was not so high as to be noxious or primarily trigeminal in nature. The odorants are shown in Table 1.

Each mask was worn for 1 minute, and brachial penile index was then recorded. There was then a 3-minute "washout" period between masks which involved breathing filtered air in a relative odor-free environment. At the end of the testing, an additional blank mask was worn for 1 minute, and a brachial penile index recorded. The effects of the odors were assessed by comparing brachial penile index with each individual odor as compared to the average of the control masks.

Statistical Analysis. The statistical analysis was provided by Sally Friels, Ph.D. of the University of Illinois School of Public Health, Chicago, Ill. Statistical significance was defined if a p value was less than or equal to 0.05. Data analysis included the following nonparametric tests: Signed Rank test, Wilcoxan Rank Sum Test, and Spearman's Rank Correlation Coefficient (T. Colton, *Statistics in Medicine*, Little Brown & Co., Boston, Mass. (1974)); E. L. Lehmann, *Nonparametrics: Statistical Methods Based on Ranks*, Holden-Day, New York, N.Y. (1975)).

Demographics. GENERAL: 77.4% (n=24) of the male subjects were single, 16.1% (n=5) were married, and 6% (n=2) were divorced. All subjects lived in Chicago and surrounding suburbs. Subjects were recruited through radio solicitation. All subjects were literate in English.

OLFACTION: In response to the questionnaire, 55% (n=17) of the subjects admitted to olfactory evoked nostalgic experience (A. R. Hirsch, *Advances in Consumer Research* 19:390–395 (1992)). 61% (n=19) did not smoke, 29% (n=9) smoked one ore less than one pack per day, and 10% (n=3) smoked between 1.1 to 2 packs per day. Given age and sex, UPSIT scores were graded based on published normal values (Doty et al., *Chemical Sense* 10:297–300 (1985)). Given these, 51% (n=16) had normal olfactory ability, whereas 48% (n=15) were microsmic or anosmic. 71% (n=22) customarily wore cologne. Of those who currently had regular sexual partners (n=23), 83% (n=19) of their partners customarily wore perfume or cologne.

SEXUAL: 74% (n=23) of the subjects had at least one regular sexual partner. None admitted to erection difficulties in the last 30 days. The frequency of intercourse over the last 30 days varied from zero in 19% (n=6) to 25 in 6% (n=2) described as having more than one sexual partner in the last 30 days. 87% (n=27) described heterosexual preference, whereas 13% (n=4) had homosexual preference. In describing level of sexual satisfaction on a scale of one to five, with five being most satisfied, 23% (n=7) described a maximum level of sexual satisfaction whereas 6.5% (n=2) described the lowest level of satisfaction with a median of three. As a means of assessing physiologic erectile function, frequency of morning erections was obtained. These were rated on a scale of one to five, one being absent and five being every morning. While 6% (n=2) described erections every morning, 3% (n=1) described the absence of morning erections, with a median of three. Most stated that odors never induced an erection (84%, or n=26), while 16% (n=5) admitted to odor-induced erection.

Results. The results are shown in Table 1 below. Sources of the odorants were Energy Essentials, IFF, AromaTech and essential oils.

The mixture of lavender and pumpkin pie odorants produced the greatest increase in median penile blood flow (40%). This was followed by the combination of black licorice and doughnut (31.5%), followed by pumpkin pie and doughnut (20%). The odor with the least effect on the median penile brachial index was cranberry which increased blood flow by 2%. Despite our hypothesis, no odor was found that reduced penile blood flow.

TABLE 1

Odorant/Odorant Mixture	Median*
Lavender and pumpkin pie	0.4000
Doughnut and black licorice	0.3150
Pumpkin pie and doughnut	0.2000
Orange	0.1950
Lavender and doughnut	0.1800
Black licorice and cola	0.1300
Black licorice	0.1300
Doughnut and cola	0.1250
Lily of the valley	0.1100
Buttered popcorn	0.0900
Vanilla	0.0900
Pumpkin pie	0.0850
Lavender	0.0800
Musk	0.0750
Cola	0.0700
Doughnut	0.0700
Peppermint	0.0600
Cheese pizza	0.0500
Roasting meat	0.0500
Parsley	0.0450

TABLE 1-continued

Odorant/Odorant Mixture	Median*
Cinnamon buns	0.0400
Green apple	0.0375
Rose	0.0350
Strawberry	0.0350
Oriental spice	0.0350
Baby powder	0.0325
Floral	0.0300
Chocolate	0.0275
Pink grapefruit	0.0250
Cranberry	0.0200

*Median penile blood flow

In those with normal olfactory ability, significant increase in brachial penile index correlated with (1) age and response to vanilla ($p=0.05$), (2) self assessed level of sexual satisfaction and response to strawberry ($p=0.05$), and (3) frequency of sexual intercourse and response to lavender ($p=0.03$), oriental spice ($p=0.02$) and cola ($p=0.03$).

Discussion. Although it was hypothesized that an odorant would be found that would reduce penile blood flow, no such odorant was identified. Such an odorant could be utilized to help decondition sex offenders. The results show that a hedonically positive odorant increased penile blood flow.

The present odors are not considered human pheromones which are believed to act upon the brain to cause an endocrinologic effect. Unlike pheromones, the present odorants that affected penile blood flow act immediately on the brain rather than in the slow manner of pheromones, or have an immediate psychological effect upon the brain.

There are several mechanisms by which the odorants may have affected penile blood flow. The odorants may have induced a Pavlovian conditioned response that reminded the subject of their sexual partners or their cooking and the associated mood states. Alternatively, odors may have induced a state of olfactory evoked recall. In a study of 989 people from 45 states and 39 countries, it was found that the odor that most induced olfactory evoked nostalgia response in those raised in the United States was that of baked goods (A. R. Hirsch, *Advances in Consumer Research* 19:390–395 (1992)). Although not wished to be held to any theory, odors that induced a nostalgic response and the associated positive mood state may have impacted upon penile blood flow. Or, the odors may have induced relaxation. Green apple has been suggested to reduce anxiety, and lavender, which increases alpha waves posteriorly, has been associated with a relaxed state (H. Sugano, *JASTS* XXII:8 (Abstract) (1988); J. R. King, "Anxiety reduction using fragrances," in *The Psychology and Biology of Fragrance*, pages 147–165, Van Toller and Dodd (eds.), Chapman and Hall, Ltd., London (1988)). Under a condition of reduced anxiety, inhibitions may have been removed and penile blood flow increased.

Alternatively, odors may have awakened the reticular activating system. Studies have indicated that jasmine increases beta waves frontally, and this is associated with a more alert state (Sugano (1988), supra). By making an individual more awake and alert, the odors may have caused subjects to be more aware of their entire environment, including any sexual cues around them, thus increasing penile blood flow.

Another possible mechanism is that the odorants may have acted neurophysically. It has been demonstrated that stimulation of the septal nucleus in the squirrel monkey induces erection (P. D. MacLean, "Cerebral evolution of emotion," in Lewis and Haviland (eds.), *Handbook of Emotions, page* 77, The Guilford Press, New York, N.Y. (1993)). A direct pathway connects the olfactory bulb to the septal nucleus (P. D. MacLean, *A Triune Concept of the Brain and Behavior*, page 14, University of Toronto Press, Toronto (1973)). Thus, it appears anatomically correct that odor may impact upon the septal nucleus and induce erection with associated increase in penile blood flow.

A direct physiologic mechanism may also play a role in the present method. One subject slept through the entire testing period, yet still showed the greatest increase in penile blood flow with the odors of the combination of lavender and pumpkin pie.

Alternatively, increased aggression through septal nucleus stimulation may be the primary effect. The increased penile blood flow may act not as a measure of direct sexual excitation, but may be the result of a "neighborhood effect" of induced aggression (Donatucci and Lue, "Physiology of Penile Tumescence," in *The Penis*, page 19, Hashmat and Das (eds.), Lea and Febiger, Philadelphia, Pa. (1993)).

In addition, a generalized parasympathetic effect, rather than specific sexual excitation, may act to increase penile blood flow. Primitive humans congregated around food kills, and there they had the greatest chance to procreate (J. Diamond, *The Third Chimpanzee: the evolution and future of the human animal*, page 68, Harper Collins Publisher, New York, N.Y. (1992). Thus, an increase in penile blood flow in response to food odors may have held a selective advantage for survival, and such a trait would be selected for through evolution.

Neuromechanisms for sexual excitation and penile erection. All natural functions are controlled by the nervous system, and the sexual response cycle is ultimately dependent on an intact neurophysiologic substrate. The sexual action can be viewed in the framework of Sherrington's reflex arc as a complicated knee jerk (W. Pryse-Phillips, *Companion to Clinical Neurology*, pages 785–786, Little, Brown and Company, Boston, Mass. (1995)).

There are several components that are involved. There is an afferent component of the sexual reflex arc which is activity by a diverse variety of exogenous stimuli: the primary stimulus consists of erotic visual, auditory, olfactory and tactile sensations. In addition, internal imagery, as well as REM periods of sleep, can serve as a primary stimulus of the sexual reflex. Each of these modes of activation act through different locations in the nervous system throughout the body. These stimuli are processed through specialized areas of the neocortex, limbic system and spinal cord, and then input into a final common pathway of sexual behavior. The efferent limb of the reflex arc involves a synchronized response of the voluntary and autonomic nervous system. Sexual stimulating odors rapidly traverse the afferent arc entering the limbic system and its neocortical connections.

There is also evidence that indicates that there is a direct connection between the olfactory bulb and the vomeronasal organ of the brain. In subhuman primates, the vomeronasal is where pheromones act (E. B. Keverne, "Pheromones and sexual behavior," in *Handbook of Sexology*, Money and Musaph (eds.), Elsevier/Horth-Holland Biomedical Press (1977)).

Thus, there are several pathways through which odors may impact upon sexual function. These pathways include: inducing memory through hippocampi connections, inducing direct penile effects through olfactory bulb septal nuclei connections, and/or affecting potential pheromonal action on the hypothalamus via the vomeronasal organ.

What is claimed is:

1. A method of increasing penile blood flow in a male individual, comprising:

administering to the male by inhalation of an odorant in an amount effective to increase penile blood flow;

the odorant selected from the group consisting of orange, a mixture of lavender and pumpkin pie a mixture of doughnut and black licorice, a mixture of pumpkin pie and doughnut lily of the valley, black licorice, a mixture of doughnut and cola, a mixture of black licorice and cola, a mixture of lavender and doughnut, chocolate, strawberry, rose, green, apple, parsley, peppermint, musk lavender, vanilla, cranberry, pink grapefruit, floral, baby powder, oriental spice, cinnamon buns, roasting meat, cheese pizza, doughnut, cola, pumpkin pie, and buttered popcorn.

2. A method of increasing penile blood flow in a male individual, comprising:

administering to the male by inhalation of an odorant in an amount effective to increase penile blood flow;

the odorant selected from the group consisting of a mixture of lavender and pumpkin pie, a mixture of doughnut and black licorice, and a mixture of pumpkin pie and doughnut.

3. A method of increasing penile blood flow in a mile individual, comprising:

administering to the male by inhalation of an odorant in an amount effective to increase penile blood flow;

wherein the odorant is selected from the group consisting of a doughnut odorant, a cinnamon buns odorant, a pumpkin pie odorant, a cola odorant, and an odorant mixture comprising one or more of those odorants.

4. An article of manufacture, comprising:

(a) an odorant as recited in claim 1 packaged within a container, wherein the odorant when inhaled by a male individual is effective to increase penile blood flow; and

(b) instructions for use of the odorant according to the method of claim 1.

5. An article of manufacture, comprising:

(a) an odorant as recited in claim 2 packaged within a container, wherein the odorant when inhaled by a male individual is effective to increase penile blood flow in the male; and

(b) instructions for use of the odorant according to the method of claim 2.

6. An article of manufacture, comprising:

(a) an odorant as recited in claim 3 packaged within a container, wherein the odorant when inhaled by a male individual is effective to increase penile blood flow; and

(b) instructions for use of the odorant according to the method of claim 3.

7. The method of claim 1, wherein the odorant is administered in a form selected from the group consisting of a scented cloth, a liquid or solid form contained in a vessel having a cap, an aerosol spray, a pump-type spray, a nasal spray, a liquid or solid form contained in a blister pack, and microcapsules contained in a scratch-and-sniff odor patch.

8. The method of claim 1, wherein the odorant is administered in a form selected from the group consisting of a lotion, cream, perfume, and cologne.

9. The method of claim 1, wherein the odorant is administered by means of a pen-like dispenser containing the odorant in a liquid form.

10. The method of claim 2, wherein the odorant is administered in the form selected from the group consisting of a scented cloth, a liquid or solid form contained in a vessel having a cap, an aerosol spray, a pump-type spray, a nasal spray, a liquid or solid form contained in a blister pack, and microcapsules contained in a scratch-and-sniff odor patch.

11. The method of claim 2, wherein the odorant is administered in a form selected from the group consisting of a lotion, cream, perfume, and cologne.

12. The method of claim 2, wherein the odorant is administered by means of a pen-like dispenser containing the odorant in a liquid form.

13. The method of claim 3, wherein the odorant is administered in the form selected from the group consisting of a scented cloth, a liquid or solid form contained in a vessel having a cap, an aerosol spray, a pump-type spray, a nasal spray, a liquid or solid form contained in a blister pack, and microcapsules contained in a scratch-and-sniff odor patch.

14. The method of claim 3, wherein the odorant is administered in a form selected from the group consisting of a lotion, cream, perfume, and cologne.

15. The method of claim 3, wherein the odorant is administered by means of a pen-like dispenser containing the odorant in a liquid form.

16. A method of increasing penile blood flow in a male individual, comprising:

administering to the male by inhalation of an odorant in an amount effective to increase penile blood flow;

the odorant administered in a form selected from the group consisting of a scented cloth, a liquid or solid form contained in a vessel having a cap, an aerosol spray, a pump-type spray, a nasal spray, a liquid or solid form contained in a blister pack, and microcapsules contained in a scratch-and-sniff odor patch; and

the odorant selected from the group consisting of orange, a mixture of lavender and pumpkin pie, a mixture of doughnut and black licorice, a mixture of pumpkin pie and doughnut, lily of the valley, black licorice, a mixture of doughnut and cola, a mixture of black licorice and cola, a mixture of lavender and doughnut, chocolate, strawberry, rose, green apple, parsley, peppermint, musk, lavender, vanilla, cranberry, pink grapefruit, floral, baby powder, oriental spice, cinnamon buns, roasting meat, cheese pizza, doughnut, cola, pumpkin pie, and buttered popcorn.

17. The method of claim 16, wherein the odorant is administered in a form selected from the group consisting of a lotion, cream, perfume, and cologne.

18. The method of claim 16, wherein the odorant is administered by means of a pen-like dispenser containing the odorant in a liquid form.

19. A method of increasing penile blood flow in a male individual, comprising:

administering to the male by inhalation of an odorant in an amount effective to increase penile blood flow;

the odorant administered in a form selected from the group consisting of a scented cloth, a liquid or solid form contained in a vessel having a cap, an aerosol spray, a pump-type spray, a nasal spray, a liquid or solid form contained in a blister pack, and microcapsules contained in a scratch-and-sniff odor patch;

the odorant selected from the group consisting of orange, a mixture of lavender and pumpkin pie, a mixture of doughnut and black licorice, a mixture of pumpkin pie and doughnut, lily of the valley, black licorice, a mixture of doughnut and cola, a mixture of black licorice and cola, and a mixture of lavender and doughnut.

20. The method of claim 19, wherein the odorant is administered in a form selected from the group consisting of a lotion, cream, perfume, and cologne.

21. The method of claim 19, wherein the odorant is administered by means of a pen-like dispenser containing the odorant in a liquid form.

22. An article of manufacture, comprising:

(a) an odorant as recited in claim 16 and packaged in a recited form, wherein the odorant when inhaled by a male individual is effective to increase penile blood flow; and

(b) instructions for use of the odorant according to the method of claim 16.

23. An article of manufacture, comprising:

(a) an odorant as recited in claim 19 and packaged in a recited form, wherein the odorant when inhaled by a male individual is effective to increase penile blood flow; and

(b) instructions for use of the odorant according to the method of claim 19.

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United States Patent [19]

Hirsch

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[54] **METHOD OF ALTERING PERCEPTION OF RELATIVE SPACE OF AN AREA**

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[52] **U.S. Cl.** **424/47**; 514/957

[58] **Field of Search** 514/957; 424/47

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[57] **ABSTRACT**

The present invention provides a method for altering a person's perception of a confined or open space by administering an odorant substance to the person.

18 Claims, No Drawings

METHOD OF ALTERING PERCEPTION OF RELATIVE SPACE OF AN AREA

BACKGROUND OF THE INVENTION

Individual tolerance of spatial size varies from the extremes of claustrophobia (the fear of closed or narrow spaces) to agoraphobia (the fear of open spaces). The everyday lives of persons with spatial anxiety can be dramatically affected. Those with severe claustrophobia fear everyday activities such as riding in elevators, buses, and subways. Those with agoraphobia may have difficulty leaving their homes. Claustrophobia, based on community samples, ranges from about 10 to 11.3%. The calculated lifetime prevalence of agoraphobia is between about 0.5% and 1.7%. A person with claustrophobia or agoraphobia experiences panic attacks when in a small, confined area or in an open space, respectively. The panic attack can result in a physiological response including an increased heart rate, sweaty palms, trembling and shortness of breath.

Entire courses in interior design and architecture have focused upon influencing perceptions of surrounding space, and countless resources are spent to expand cramped offices and shrink vast convention halls. Visually, a cramped room can be enlarged, for example, through the use of mirrors, windows and/or natural light, and by positioning furniture along the periphery. The visual image can also be used to lessen the expanse of a large room, for example, by using curtains, dim lights and/or ornate designs, and by placing furniture in the middle of the room.

Auditory stimuli, such as echoes, can also affect judgment of room size. Bare walls that increase echoes can make a room seem larger. In contrast, carpets and padded walls can dampen sound and make the room seem smaller.

The sensation of touch can also influence perceived room size. Hardwood floors can enlarge a small interior while plush carpeting and oversized furniture can decrease the expanse of larger interiors.

Perceptions of room size can also be influenced by temperature. A warm fireplace can impart a cozy feeling in a large living room. An extreme temperature, such as a frigid parking garage in winter, can increase feelings of solitude and emptiness. In contrast, an oppressive summer heat can induce a feeling of confinement, particularly when stalled in a traffic jam.

Although such design changes can alter a person's perception of room size to lessen the feelings of claustrophobia and agoraphobia, persons suffering from such ailments cannot rely on such alterations in every instance. Therefore, an object of the invention is to provide a means to enable a person suffering from a spatial tolerance disorder to better tolerate a closed/narrow space or open space. Another object of the invention is to provide such means in a form that is portable and can be carried by the individual for ready access and use.

SUMMARY OF THE INVENTION

The present invention provides a method for treating a patient having a spatial dissonance by administering an odorant substance that will alter the patient's perception of relative space of an area. An odorant substance can be administered to expand a person's perception of a cramped and/or confined space or to diminish his or her perception of a wide or vast space.

According to the invention, a substance having the characteristics of a green apple odorant, cucumber odorant, or seashore odorant is administered to a patient to cause the patient's perception of a confined area to become altered and expanded, preferably using a green apple odorant. The invention further includes administering a substance having the characteristics of a barbecue smoke odorant to a patient to cause the patient's perception of an open area to become altered and diminished.

The introduction of a space perception altering odorant can be used to decrease the anxiety felt by claustrophobic and agoraphobic persons and thereby help them to more easily assimilate into an everyday environment. The introduction of a space perception altering odorant can also be used to comfort persons who do not have the extreme anxiety characteristic of claustrophobia or agoraphobia, but experience a mild spatial dissonance, by modifying the ambience of everyday surroundings and changing their perception of relative space.

DETAILED DESCRIPTION OF THE INVENTION

According to the invention, it was found that the administration of a green apple odorant substance will expand the perception of room size for a person suffering from claustrophobia. In particular, it was found that a green apple odorant can decrease the anxiety in a person suffering from claustrophobia, or other like phobia, and/or reduce the stress experienced by a person with mild spatial dissonance of closed or narrow space. Examples of such confined spaces include an enclosed room, closet, telephone booth, elevator car, train compartment, airplane compartment, automobile interior, subway compartment, and the like. While not as dramatic of an impact as green apple, seashore and cucumber odorant substances can also be used to increase or expand the perception of room size.

It was further found that administration of a barbecue smoke odorant substance will diminish perception of room size or space of an area, for a person suffering from agoraphobia or other like phobia. A barbecue smoke odorant can therefore be used to reduce the anxiety felt by a person suffering from agoraphobia, and/or reduce the stress experienced by a person with a mild spatial dissonance of open space such as a convention hall, interior of a mall, hallway, concert hall, out-of-doors expanse, and the like.

Such odorants are commercially available, for example, from International Flavors and Fragrances, Inc. (IFF), New York, N.Y.

According to the invention, the odorant substance is dispensed in an amount and time effective to provide a vaporous emission for inhalation by the patient to effectively change the patient's perception of space and reduce anxiety of the patient having a stress reaction due to a spatial dissonance. Such an effect can be assessed and measured subjectively by interviewing and questioning the patient about their perception of relative space before and after the administration of the odorant substance, and assessing their response according to an analog rating scale, for example, a scale of 1–5 wherein 1=confined and 5=roomy.

The odorant can be dispensed by means of a scented cloth such as a fragranced surgical mask, a vessel containing the odorant substance, optionally with a valve and nozzle mechanism for dispensing the substance, a blister pack containing a preparation of the odorant, an aerosol or non-aerosol spray, a gas, a solid or liquid air freshener, a scented cloth, lotion, cream, perfume, cologne, potpourri, incense, lightbulb ring, a candle, fabric softener, carpet shampoo or freshener, a plug-in air freshener, scratch-and-

sniff odor patches containing microcapsules of the odorant, and the like. The odorant substance can be administered in combination with an odorless liquid carrier such as mineral oil or water, and can be formulated with a viscosity effective to allow for aerosolization.

The odorant can be provided in a portable dispenser for ready individual use, for example, by means of a blister pack, a small vial of lotion, a booklet of scratch-and-sniff odor patches, and the like, that include an effective amount of the desired odorant substance. An odorant substance can also be administered to a group of people within a confined area, for example, by pumping air containing the odorant substance through an air vent, spraying the odorant substance into the air as a mist or dry powder using an aerosol or non-aerosol spray, or by placing the odorant substance as a solid or liquid in the room such as a solid or liquid air freshener, scented candle, carpet freshener, and the like.

The odorant substance can be packaged as a part of an article of manufacture, or kit. The kit can include in association, for example, (a) the odorant substance, carrier and other optional additives for forming a composition, placed in containing means such as a vial, jar, pouch, can, bottle, cloth, aerosol can, blister pack, and the like, containing an effective amount of the odorant substance; and (b) means for instructing as to the odorant substance and its use for treating a spatial dissonance to alter a perception of room size. The parts of the kit can be contained or separately packaged within a packaging material, such as a box or bag.

EXAMPLE

Subject evaluation.

Eight subjects, four females and four males, aged 18 to 64 years (mean =30.9, median 19), underwent a series of olfactory and psychological tests. Formal olfactory tests included Pyridine Threshold Test of Amoore, Unilateral Thiophane Threshold Test of Amoore, and the University of Pennsylvania Smell Identification Test (Hirsch et al., *Chemical Senses* 17: 643 (1992); Amoore et al., *Rhinology* 21:49–54 (1983); and Doty et al., *Chemical Senses* 10:297–300 (1985), respectively). All were performed according to standard test procedures.

Olfactory test results were as follows: on the threshold test of Amoore, five subjects scored 100%, two scored 90%, and one scored 80%. UPSIT scores ranged from 19 to 37. Subject number 2 scored hyposmic (diminished sense of smell) on this test as adjusted for age and sex. The seven remaining subjects had UPSIT scores ranging from 29 to 37 (TABLE 1). Olfactory threshold ranged from −5 to 20 decismels with an average for the left nostril of 11.9 and for the right nostril of 10 decismels, all within the normal range (TABLE 1).

TABLE 1

OLFACTORY TEST SCORES

Subject	1	2	3	4	5	6	7	8
Threshold Tests of Amoore								
Score	90%	100%	100%	100%	100%	90%	80%	100%
UPSIT								
Score	36	19*	29	35	36	37	37	34
Olfactory Threshold								
Right	−5	15	20	10	10	5	15	10
Left	15	10	10	10	15	5	20	10

*Hyposmic

The following standardized self evaluations were also administered: Zung Self-Rating Depression Scale, Zung Anxiety Inventory, and Beck Depression Inventory (W. W. K. Zung, *Arch. Gen. Psychiatry* 12:63–70 (1965); W. W. K. Zung, *Psychosomatics* 12(6):371–379 (1971); Beck et al., "Assessment of Depression, Depression Inventory: Psychological Measurements in Psychopharmacology," in *Modern Problems in Psychopharmacology* (9th ed.), Pinchot et al. (ed.) (1974), respectively). Claustrophobia, phobia, and spatial anxiety were assessed using detailed self-evaluation questionnaires devised from a checklist integrating criteria specified by DSM-IV for diagnoses of panic disorder, anxiety disorders, and specific phobia (American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.), at pages 393–444, Washington, D.C., American Psychiatric Association (1994)). The subjects were also assessed according to standard questionnaires including Anxiety Status Inventory and the SCL-90R (Bystritsky et al., "Development of a Multidimensional Scale of Anxiety," *J. of Anxiety Disorders* (19___); L. R. Derogatis, The SCL-90R, Baltimore Clinical Psychometric Research (1977)). Also used was a compendium of several questionnaires based on claustrophobia (C. B. Scrignar, "Stress Strategies," *The Treatment of the Anxiety Disorders*, pages 6–7, S. Karger Basel (1983); Clarke et al., *Hypnosis and Behavior Therapy, The Treatment of Anxiety and Phobias*, pages 320–321, Springer Publishing Company, New York, N.Y. (1983); World Psychiatric Association, *Panic Anxiety and its Treatments*, page 7, Klerman et al. (eds.), American Psychiatric Press, Inc., Washington, D.C. (1993)). The questionnaire on claustrophobia also included a differentiation between "suffocating" and "restricting" claustrophobia (Rachman et al., "Analyses of Claustrophobia," *J. Anxiety Disorders*, pages 281–291, Pergamon Press Ltd. (1993)).

The psychological test scores showed that four subjects were at least somewhat anxious, of which one was depressed and another was slightly to moderately depressed (TABLE 2). Zung anxiety scores averaged 34.5 and ranged from 20 to 42 (less than 36 being normal). Zung depression scores averaged 34.4 and ranged from 24 to 46 (less than 40 being normal). Beck depression scores averaged 6.6 and ranged from 0 to 16 (14 or less being normal).

TABLE 2

PSYCHOLOGICAL TEST SCORES

	Subjects							
	1	2	3	4	5	6	7	8
*Zung Anxiety	39	20	42	37	32	42	33	31
**Zung Depression	35	24	43	32	33	46	34	25
***Beck Depression	11	0	10	6	4	16	4	2

*Normal = <36.
**Normal = <40.
***Normal = 14 or less.

Of the eight subjects, four were single. While one smoked cigarettes, none used drugs or medications.

In assessing individual variations in smell awareness, subjects were queried as to their perceptions of both their own personal odor and the odors around them, as well as their use of cosmetic and hygienic fragrances. One subject considered his sense of smell as excellent, while all others described their olfactory ability as normal. On a scale from 1–10, with 10 being the highest, subjects rated the importance of their sense of smell as 7 on average, with a range of 3–10.

In assessing perception of personal odor, five characterized the odor about them as pleasant, and three subjects considered their own smell as neutral or provided no response to the question. The general perception of a pleasant self odor correlated with personal fragrancing. Six of the eight subjects used commercial perfumes or colognes, and breath fresheners including mints and mouthwash, while two did not. In addition, while all eight subjects used a deodorant, the six subjects who used a perfume or cologne also used a scented deodorant. The two subjects who used no perfume, used an unscented deodorant.

The subjects were also questioned about external odors (those not from their natural body odor or personal fragrancing). Five subjects considered persons around them as having a pleasant smell, two were neutral about other people's odors and one subject perceived people around them as having an unpleasant smell. When questioned about the use of potpourri or room fresheners, four subjects were found to use such fresheners, three did not, and one gave no response.

Collection of Data

To assess initial perceptions of spatial size, the subjects completed a questionnaire including a 9-centimeter analog scale to rate the feeling of room size. This was performed twice, each time in a clinically odor-free environment: once in a 12 ft. by 9 ft. by 9 ft. examining room, and a second time in a cylindrical space-deprivation booth 2.5 ft. in diameter by 4.5 ft. in height. After sitting confined for one minute in the booth, subjects then donned unfragranced surgical masks. After 30 seconds wearing the masks, they again completed the analog scale. The masks were then removed for a two-minute odorless hiatus in the booth. The same procedure was repeated ten times using surgical masks with ten different fragrances applied.

The following fragrances were tested: evergreen (International Flavors and Fragrances, Inc. (IFF)); barbecue smoke (IFF 2247-HS); Tranquilities perfume (Elizabeth Arden); vanilla (Florasynth, Inc., New York, N.Y.; AE-3899); buttered popcorn (Florasynth; AG-6958 (GRAS)); seashore (IFF); charcoal-roasting meat combination (IFF 2189-HS); cucumber (IFF); coconut (IFF); and green apple (IFF).

One to two drops of each odorant were placed on each surgical mask, producing odor levels considered hedonically acceptable by a sensory panel consisting of staff from the Smell & Taste Treatment and Research Foundation. Although the odorant substance was administered using a fragranced surgical mask in the experiment, it is understood that a variety of shapes, sizes and configurations may be accommodated for the administration of the odorant substance according to the invention.

The perfumed masks were presented in a random, double-blind manner. Afterwards, subjects rated the familiarity of the odors and their hedonics (pleasant or unpleasant) on analog scales. Following testing of a fragrance mask, another unfragranced mask was applied for evaluation. Statistical analysis was then performed based on Signed-Rank test for pair differences (E. L. Lehmann, *Nonparametrics: Statistical Methods Based on Ranks*, Holden-Day (1975)).

Odors were classified two ways: "indoor" versus "outdoor" (TABLE 3), and as "food" versus "nonfood" (TABLE 4).

TABLE 3

CLASSIFICATIONS OF ODORS

Indoor	Outdoor
Barbecue Smoke	Evergreen
Vanilla	Tranquilities
Buttered Popcorn	Seashore
Charcoal Roasting Meat	Cucumber
	Coconut
	Green Apple

TABLE 4

CLASSIFICATIONS OF ODORS

Food	Non-Food
Barbecue Smoke	Evergreen
Vanilla	Tranquilities
Buttered Popcorn	Seashore
Charcoal Roasting Meat	Green Apple
Cucumber	
Coconut	

The effect of each odor on perception of room size was calculated for each of the eight subjects. This was done by first computing the average score on analog scales of room size for the two blank masks. This average score was then used as a baseline from which to determine the shift due to the presence of each of the odors (TABLE 5). This odor-induced shift was also calculated for the seven subjects defined as normosmics (having a normal sense of smell) based on the UPSIT and for the six subjects who were found to use personal fragrancing.

TABLE 5

EIGHT SUBJECTS' SHIFTS ON ANALOG SCALE OF ROOM SIZE WITH TEN ODORS

	Subjects							
Odors	1	2	3	4	5	6	7	8
Evergreen	−.25	0	−1	−2.5	2	.25	2.5	.5
Barbecue Smoke	−.25	0	−1	−.5	−1	−.25	−1	.5
Tranquilities	.25	0	0	−2	0	−.75	3	.5
Vanilla	.25	0	−1	−1.5	−1	−.75	3	0
Buttered Popcorn	−.25	0	0	−2.5	−.5	−.25	3.5	.5
Seashore	−.25	0	−.5	−2	.5	−.75	2.5	2
Charcoal Roasting Meat	−.25	0	.5	−1.5	−.5	−.75	2.5	.5
Cucumber	−.25	0	−1	−1.5	−1	.25	3	0
Coconut	−.25	0	−.5	2	−2	−.25	−3	.5
Green Apple	−.25	0	.5	−.5	1.5	.25	3	.5
	Subjects Characteristics							
Age								
Sex								
Good ability to smell	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Use perfume	No	No	Yes	Yes	Yes	Yes	Yes	Yes

For each subject, a change from baseline was detected for each odor. Additionally for each subject, the change from baseline of each odor was contrasted with the median change from baseline for the other nine odors tested. In this fashion, every odor was tested for each individual. Hence, for each individual, calculations were made for the difference between the analog shift for each odor and the mean of the analog shifts for the other nine odors.

The median change for each odor from calculated baselines for each subject was determined. The same method was

used to find the median for the other nine odors across all subjects. Then the significance of this difference was determined between these medians (TABLE 6). In a similar fashion, significance was determined for all normosmic subjects as determined by the UPSIT (n=7) (TABLE 7), and for those who used personal fragrancing (n=8) (TABLE 8).

TABLE 6

COMPARISONS OF MEDIANS OF ODOR SHIFTS FROM BASELINE VERSUS MEDIANS OF BASELINE SHIFTS FOR THE OTHER NINE ODORS ALL SUBJECTS (n = 8)
Each odor versus all others:

Odor	Signed-Rank Test p-value
Evergreen	.9844
Barbecue Smoke	.0469*
Tranquilities	.5469
Vanilla	.8438
Buttered Popcorn	.7427
Seashore	.5469
Charcoal Roasting Meat	.9453
Cucumber	.9453
Coconut	.7427
Green Apple	.1484

*Significantly lower than the average of all others

TABLE 7

COMPARISONS OF MEDIANS OF ODOR SHIFTS FROM BASELINE VERSUS MEDIANS OF BASELINE SHIFTS FOR THE OTHER NINE ODORS NORMOSMIC SUBJECTS AS DETERMINED BY UPSIT (n = 7)
Each odor versus all others:

Odor	Signed-Rank Test p-value
Evergreen	.9844
Barbecue Smoke	.0625*
Tranquilities	.1563
Vanilla	.8125
Buttered Popcorn	.2969
Seashore	.1563
Charcoal Roasting Meat	.4688
Cucumber	.6875
Coconut	1.0000
Green Apple	.0156**

*Lower, but no longer significantly lower than the others.
**Significantly higher than the average of all the others.

TABLE 8

COMPARISONS OF MEDIANS OF ODOR SHIFTS FROM BASELINE VERSUS MEDIANS OF BASELINE SHIFTS FOR THE OTHER NINE ODORS SUBJECTS WHO USE PERSONAL FRAGRANCE (n = 6)
Each odor versus all others:

Odor	Signed-Rank Test p-value
Evergreen	1.0000
Barbecue Smoke	.0938*
Tranquilities	.3125
Vanilla	1.0000
Buttered Popcorn	.4375
Seashore	.2188
Charcoal Roasting Meat	.5625
Cucumber	.8438
Coconut	.8438
Green Apple	.0313**

*Lower, but not significantly lower than the others.
**Significantly higher than the average of all the others.

Further, medians were also compared differentiating odors based on hedonics, recognition, and odor classification (i.e., indoor versus outdoor, food versus nonfood) for all subjects, normosmics and those using personal fragrancing, and p-values were computed in the same manner (TABLE 9).

TABLE 9

P-VALUES FROM THE SIGNED-RANK TEST FOR PAIRED DIFFERENCES

	All Subjects	Normosmics	Personal Fragrance Users
Like vs. Dislike	.3125	.3125	.4375
Recognize vs. Fail to Recognize	.1563	.1563	.1875
Indoor vs. Outdoor	.2031	.2031	.1563
Food vs. NonFood	.1563	.1563	.2188

Data Analysis

TABLE 5 shows the shift with each odor away from the average with the odorless masks. Those with positive values made the room appear larger and those with negative values made the room subjectively smaller compared to the non-odorized condition. The odor that caused a perceptual shift that was statistically significant was the odor of barbecue smoke ($p<0.05$) which decreased the perceived size of the room.

Data was further analyzed excluding the hyposmic individual, subject 2, (UPSIT rated microsmic) and also for the six subjects who used personal fragrances (subjects 3 through 8). In both these subgroups (normosmics and personal-fragrance users), the green apple odor increased perceptions of room size. In both groups, green apple odor produced statistically significant results: in all normosmics ($p=0.03$) and in normosmic fragrance users ($p=0.02$).

The green apple odor had the most significant impact of enlarging perception of room size. Seashore and cucumber had similar effects on perception although less significant than the effect provided by the green apple odorant.

The odors had no effect on the perception of room size by the individual with poor olfactory ability based on the UPSIT. This indicates that the odors did in fact cause response to room size perception.

Thus, the invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention, and the invention is not to be construed as limited to the specific embodiments shown in the drawings.

What is claimed is:

1. A method for altering a person's perception of relative space of a confined area, comprising:

administering to the person an effective amount of a green apple odorant such that the relative space of the area is perceived to diminish.

2. The method of claim 1, wherein the confined area is selected from the group consisting of a room, closet, telephone booth, elevator car, train compartment, airplane compartment, automobile interior, subway compartment.

3. The method of claim 1 further comprising questioning the person before and after administering the odorant to assess the effect of the odorant on the person's perception of the area.

4. The method of claim 1, wherein the method comprises administering the odorant in a form selected from the group

consisting of a spray, gas, scented cloth, lotion, cream, perfume, cologne, scratch-and-sniff odor patch containing microcapsules of the odorant, a blister pack containing the odorant, solid air freshener, potpourri, incense, lightbulb ring, candle, fabric softener, carpet freshener, and combinations thereof.

5. The method of claim 1, wherein the method comprises administering the odorant to a group of patients.

6. The method of claim 1, wherein the method comprises administering the odorant by pumping a gas containing the odorant through an air vent into a room.

7. The method of claim 1, wherein the method comprises administering the odorant by spraying the odorant substance into the air.

8. The method of claim 1, wherein the method comprises administering the odorant in combination with an odorless liquid carrier.

9. The method of claim 8, wherein the viscosity of the odorant in the carrier is effective to allow for aerosolization, and the method comprises administering the odorant by spraying the odorant substance.

10. A method for altering a person's perception of relative space of an area, comprising:

administering to the person an effective amount of a barbecue smoke odorant such that the relative space of the area is perceived to diminish.

11. The method of claim 10, wherein the area is selected from the group consisting of a convention hall, interior of a mall, hallway, concert hall, a roadway.

12. The method of claim 10, further comprising questioning the person before and after administering the barbecue smoke odorant to assess the effect of the odorant on the person's perception of the area.

13. The method of claim 10, wherein the method comprises administering the odorant in a form selected from the group consisting of a spray, gas, scented cloth, lotion, cream perfume, cologne, scratch-and-sniff odor patch containing microcapsules of the odorant, a blister pack containing the odorant, solid air freshener, potpourri, incense, lightbulb ring, candle, fabric softener, carpet freshener, and combinations thereof.

14. The method of claim 10, wherein the method comprises administering the odorant to a group of patients.

15. The method of claim 10, wherein the method comprises administering the odorant by pumping a gas containing the odorant through an air vent into a room.

16. The method of claim 10, wherein the method comprises administering the odorant by spraying the odorant substance into the air.

17. The method of claim 10, wherein the method comprises administering the odorant in combination with an odorless liquid carrier.

18. The method of claim 17, wherein the viscosity of the odorant in the carrier is effective to allow for aerosolization, and the method comprises administering the odorant by spraying the odorant substance.

* * * * *

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United States Patent [19]

Hirsch

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[54] **METHOD OF TREATING HEADACHES, AND ARTICLE OF MANUFACTURE THEREFOR**

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[52] **U.S. Cl.** **424/195.1**; 424/434

[58] **Field of Search** 602/74; 424/195.1, 424/434; 512/4, 5; 514/872, 929; 600/557

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[57] **ABSTRACT**

A method is provided for preventing or reducing the symptoms and/or duration of a migraine or other form of headache through the administration of a hedonically pleasant odorant that is inhaled by a person who is prone to or suffering from a headache. A preferred odorant is one having the characteristics of a green apple scent. Preferably, the person is presented with the odorant at a suprathreshold concentration, and inhales the odorant for about 5–15 minutes while in a prone position in a quiet, darkened room.

28 Claims, No Drawings

METHOD OF TREATING HEADACHES, AND ARTICLE OF MANUFACTURE THEREFOR

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Ser. No. 60/046,566, filed May 15, 1997.

FIELD OF THE INVENTION

The present invention relates to the treatment of headaches by the administration of odorants.

BACKGROUND OF THE INVENTION

Millions of Americans and people worldwide suffer from physically debilitating headaches. Symptoms can last more than an hour, and include a throbbing pain on one side of the head usually around the temple, nausea, blurring of vision, and sensitivity to light, sounds and smells. In about 10% of migraine occurrences, a visual aura such as blind spots, flickering points of light, double vision, or jagged lines, will precede the headache.

It has been speculated that vascular and neurogenic factors are responsible for migraine attacks. Migraines are known to be triggered, for example, by anxiety, shock, tension, fatigue and other stress factors, by menstruation and hormonal-fluctuation, by noise, flickering or bright lights, and by foods such as red wine, chocolate, wheat products, and those that contain additives such as MSG (canned soups, corn chips), tyramine (sour cream, parmesan cheese, soy sauce), and nitrites (cured meats, e.g., bacon, ham).

The aggravating effect of certain odors on migraine headaches has been documented in several studies. Blau and Solomon interviewed fifty migraine patients. Twenty of the fifty patients experienced osmophobia due to a variety of odors ranging from general cooking odor to wash-up liquid odor. Eleven patients reported that similar smells also triggered migraine headaches (Blau, et al., *J. of Neurology,* 232 (1985): 275–276). In another study, perfume and cigarette smoke triggered migraine headaches (Raffaeli, et al., *Functional Neurology* 1 (1986): 275–276). Blau's study on migraine triggers showed that certain foods induced migraines while non-migraine headaches were unaffected by them (Blau, J. N., *The Lancet* 339 (1992): 1203).

Studies have also shown smells to be part of migraine auras. Wolberg and Ziegler have reported a case of a woman who experienced olfactory hallucinations involving decaying animals before experiencing migraines (Wolberg, et al., *Arch. Neurol.* 39 (1982): 392). Crosley and Dhamoon described a mother and her daughter smelling odors similar to burning wood chips as a part of their aura (Crosley, et al., *Archives of Neurology* 40 (1983): 459). Diamond et al. mentions a woman who smelled cigarette smoke before, during and after her migraine headache even though she was not a smoker and was not around anyone who smoked (Diamond S. et al., *N. Engl. J. Med.* 312 (1985): 1390). Three migraine patients in Fuller and Guiloff's study reported smelling peanut butter and cigars (Fuller, et al., *Neurol. Neurosurg. Psych.* 50 (1987): 1688–1690). Morrison and Price found that 13% of their subjects experienced gustatory hallucinations during migraine attacks (Morrison, et al., *Psychology Medicine* 19 (1989): 919–925).

Conventional treatments for migraines are directed to oral medications to prevent the headache or reduce the symptoms. Examples include migraine abortives such as ergotamines and sumatriptan, preventatives such as antidepressants and calcium channel blockers, analgesic pain reducers (Tylenol™), and anti-nausea drugs. The ingestion of herbal solutions and teas has also been suggested, such as those made from feverfew, wood betony, chamomile, valerian root, and others. Also disclosed are various liquid formulations that are dispensed to the nasal cavity or directed to the respiratory passages to prevent recurring headaches (U.S. Pat. Nos. 5,554,639 and 5,008,289). Other treatments involve biofeedback, acupuncture, and meditation.

None of the currently known or used treatments for migraine headaches provide consistently effective therapy for preventing or reducing the pain and other symptoms of a migraine headache. A significant drawback of current treatments is the use of drugs and other chemical substances that must be ingested or applied to mucosal tissue for absorption into the bloodstream.

A survey of 109 migraine patients by Blau revealed that fifty patients could tolerate eating and drinking during migraines. Of the fifty patients, twenty-seven patients reported that eating reduced the severity and the length of migrainous symptoms. Five patients actually reported having cravings for certain foods. The patients in the study ate mostly starchy foods during attacks (Blau, J. N., *Cephalalgia* 13 (1993): 293–295). The reason these foods were effective in reducing headache may have been due to the retronasal smell provided during chewing.

Studies have shown that ambient odors can reduce anxiety and change emotions (King, J. R., *Perfumery: The Psychology and the Biology of Fragrance,* Van Toller and Dodd (eds.), London: Chapman and Hall, Ltd., 1988, pp. 147–165). Schiffman describes a study in which patients were conditioned to associate a certain odor with a relaxed state. Patients were able to reduce the severity of their anxiety episodes by inhaling their designated fragrance (Schiffman, S., *Fragrance:. The Psychology and Biology of Perfume,* Van Toller and Dodd (eds.), London: Elsevier Applied Science, 1992, pp. 57–58). In a study by Hirsch on the relationship of odors and perceptions of room size, the subjects perceived the size of a small booth to the larger after inhaling a scent similar to green apples. Hirsch speculated that the green apple scent reduced the anxiety of being enclosed in a small space and thereby increased the perceived room size (Hirsch, et al., Manuscript 1994: 2).

Therefore, an object of the invention is to provide a means that can be used by an individual to hinder or reduce the effect of a migraine headache that overcomes such shortcomings, and does not require the ingestion or absorption of a drug or other chemical substance into the bloodstream of the user. Another object is to provide an effective but simple means of treating and/or preventing a headache, particularly a severe migraine headache, and other forms of pain. Another object is to provide such means in a form that is readily available for use, and is portable and can be easily carried by the user.

SUMMARY OF THE INVENTION

These and other objects are achieved in a method of preventing or reducing the symptoms and/or duration of a migraine or other form of headache, or other form of pain, through the administration of an odorant that is inhaled by the individual.

The method involves administering an effective concentration of a hedonically positive odorant to an individual who is prone to or suffering from a migraine or other form of headache, and having the individual inhale the odorant for

an effective time period to alleviate and/or reduce cephalgic pain and other symptoms of the headache. Preferably, the subject individual is presented with the odorant at a suprathreshold concentration (e.g., about 25–55 decismel units), and inhales the odorant for about 5–15 minutes, preferably about 10 minutes. It is further preferred that the individual inhales the odorant while in a prone position, preferably in a quiet room and one that has subdued lighting or, preferably, is completely darkened.

The odorant that is administered is an aromatic substance to which the individual displays a positive hedonic response (e.g., a pleasing odor), and that provides an anxiety reducing or calming effect on the individual when inhaled. A preferred substance has the characteristics of a green apple odorant.

DETAILED DESCRIPTION OF THE INVENTION

According to the invention, it was found that the administration of a hedonically positive odorant will reduce the severity and/or duration of cephalic pain and other symptoms caused by a migraine or other form of headache. Such an odorant is one to which the individual has a pleasant or positive reaction to its scent.

According to the present method, a hedonically pleasing odorant is presented to an individual for inhaling in an amount and for a time effective to prevent, alleviate and/or reduce migrainous or other headache symptoms, which is a supra-threshold but non-irritant level of the odorant. The concentration of an odorant that is administered is preferably within a range of about 25–55 decismel units.

An example of such an odorant is a substance having the characteristic of a green apple odor such as isoamyl isovalerate. Other useful odorants include, for example, banana, peppermint, and lavender. Such odorants are available commercially, for example, from International Flavors and Fragrances, Inc. (IFF, New York, N.Y.), Energy Essentials, Aroma Tech, and as essential oils.

The odorant can be administered to an individual who is prone to migraines or other forms of headache, and/or experiencing a visual aura prior to or preceding the onset of migraine headache symptoms, as a preventative to eliminate a symptom and/or reduce the severity and/or duration of a symptom. The odorant can also be administered as a therapeutic after the onset of migrainous or other headache symptoms to reduce the severity and/or duration of a symptom.

The individual is instructed to inhale the odorant for an effective time period, preferably about 5–15 minutes, preferably about 10 minutes. It is preferred that the person is lying down in a comfortable, prone position during the inhalation period, most desirably in a room that is quiet or sound-proofed, and dimmed to totally darkened.

The method can also be used in the treatment of other forms of body pain, for example, pain associated with muscle strain, stomach cramps, surgical pain, and the like, to reduce the severity or duration of the pain that is being experienced.

An odorant or odorant mixture can be readily screened and assessed for positive hedonics and effectiveness in alleviating migrainous or other headache symptoms. For example, an odorant or odorant mixture can be administered to an individual who is questioned as to a positive or negative reaction to the pleasantness of the scent. The odorant can then be administered to the individual to assess its effectiveness in alleviating and reducing the headache symptoms.

The effect of an odorant on an individual's migraine or other headache symptoms can be assessed and measured subjectively by interviewing and questioning the individual about their symptoms before and after inhaling the odorant substance. For example, the individual can be asked whether they are experiencing a visual aura (e.g., blind spots, flickering lights, jagged lines), a pain that is more pronounced or severe on one side of the head, a pounding or throbbing head pain, head pain that disrupts their normal activity, head pain that is aggravated by activity, nausea, blurred vision, double vision, or sensitivity to light, sound or smell.

An odorant is presented at a suprathreshold level when the decismel level or concentration of the odorant is beyond that needed to be detected by a normosmic individual. At its irritative level, the odorant quantity is so high and intense that the odorant stimulates predominantly the trigeminal nerve (for pain) rather than the olfactory nerve and, hence, is perceived as noxious or painful. The irritation threshold of the patient is the lowest concentration of the substance that causes immediate stinging or burning sensations in the nose, or stinging or lacrimation of the eye. See, J. F. Gent, in *Clinical Measurement of Taste and Smell*, pages 107–166, H. L. Meiselman et al. (eds.), 602 pp., MacMillan, NY (1986); R. L. Doty et al., *Ann. Neurol.* 25: 166–171 (1989); E. Koss et al., *Neurology* 38: 1228–1232 (1988); and R. Doty, *The Smell Identification Test: Administration Manual* 1983: 13–14, Philadelphia: Sensonics, Inc. (1983).

Preferably, prior to the administration of the odorant, the individual is evaluated for olfactory capacity (e.g. loss of smell) according to an olfactory threshold test as known and used in the art. Such a test provides a precise magnitude of loss of smell and classifies the individual as normosmic, hyposmic or anosmic, which is useful in assessing the effectiveness of a particular odorant and/or the required concentration of the odorant to provide a suprathreshold level to effectively reduce migrainous symptoms. According to that test, an odorant substance such as butyl alcohol, phenyl ethyl alcohol, or pyridine, is combined in a odorless liquid medium to provide a series of dilutions, or binary steps, of the odorant. For each successive binary step up the dilution scale, the odorant is present, for example, at one half the concentration of the preceding step. The highest concentration of the odorant usually provides the substance at an irritant level. The individual is presented with the series of dilutions in ascending order, and is asked to compare each dilution step to at least one control stimulus, such as odorless propylene glycol.

Ranges of the average normal threshold for various odorant substances can be found in the art, for example, Amoore and O'Neill, "Proposal for Unifying Scale to Express Olfactory Thresholds and Odor Levels: The "Decismel Scale"," in *Proceedings of the* 1988 *Air Pollution control Association Annual Meeting*, Paper No. 78.5 (21 pp.), Air and Waste Management Association, Pittsburgh, Pa. (1988); Amoore and Haotala, "Odor as an Aid to Chemical Safety: Odor Thresholds Compared with Threshold Limit Values and Volatiles for 214 Industrial Chemicals in Air and Water Dilution," *J. Appl. Toxicology* 3(6):272–290 (1983).

In the art, a "normosmic" individual is one who can detect the odor of a substance without irritant sensations when the odorant is presented with the range of its average normal threshold. A "hyposmic" or "microsmic" individual has reduced capacity of the olfactory nerve being able to detect an odorant substance by its odor at a concentration, or decismel level, above that of a normosmic individual yet below its irritant concentration level. An "anosmic" individual is one who has essentially no olfactory nerve capacity

being unable to detect the odor of the odorant substance, but has trigeminel nerve function, being able to detect an odorant substance by means of irritant, tingling sensations when it is present at an irritant concentration. A patient who is able to detect pyridine vapor by means of irritant, tingling sensations caused by stimulation of the trigeminel nerve, but who cannot distinguish a pyridine odor at a lower concentration without such sensation, is considered to be anosmic having no olfactory nerve sensitivity.

The odorant substance is dispensed to a subject in a form that provides a vaporous emission for inhalation. The odorant substance can be administered in a liquid or solid form contained in a capped vessel, by opening a blister pack or scratch-and-sniff odor patch containing microcapsules of the odorant, as a spray from an aerosol or non-aerosol pump-type spray device, by means of a scented cloth, as a nasal spray, as a cologne or a cream, from a pen-like dispenser containing a liquid form of the odorant, and the like. It is preferred that the odorant is provided in a portable dispenser that is easily transportable and readily accessible by a person in need of relief, for example, a blister pack, booklet of scratch-and-sniff odor patches, pen-type dispenser, and the like.

The odorant substance can be packaged as part of a kit in association with a container such as a vial, jar, pouch, bottle, cloth, aerosolizer, blister pack, and the like, that held an effective amount of the odorant; and written or other form of instructions (e.g., video or cassette tape) of the use of the odorant to treat and/or prevent migraine headaches. The kit can also include a substance and instructions for testing olfactory threshold. The various parts of the kit can be packaged separately and contained within a box or other packaging material.

The invention will be further described by reference to the following detailed example. This example is not meant to limit the scope of the invention that has been set forth in the foregoing description. Variation within the concepts of the invention are apparent to those skilled in the art. The disclosures of the cited references throughout the application are incorporated by reference herein.

EXAMPLE

Use of Green Apple Odorant to Alleviate Headache

Fifty subjects with chronic cephalalgia were asked to rate the severity of their headaches at the onset and 10 minutes into three separate headache episodes. The first and third headache served as non-odor treated control headaches. During the second attack, each subject rated their headaches before and after smelling a green apple fragrance. For those with a normal olfactory ability and positive hedonics for the odorant, inhalation of the green apple odor reduced the severity of the headache as compared to the non-odor treated condition ($p<0.03$). These results indicate that green apple odorant is useful in the management of chronic headache.

Methods

Subjects. Thirty-three women and seventeen men ranging in age from 18 to 67 (mean 39) volunteered to be the subjects of this Institutional Review Board approved study. Based on their history, each subject's headache was classified into the following modified categories of the Headache Classification Committee of the International Headache Society (Headache Classification Committee of the International Headache Society, *Cephalalgia* 8 (1988 supp) 7: 1–96). traumatic (20 subjects), common migraine (14), atypical cephalalgia (10), muscle contraction (2), costens (1), pseudomotor cerebri (1), TCE headache (1) and mixed headache types (4).

Instrument. The research staff tested the subjects' olfactory ability by determining the minimal concentration of carbinol they were able to detect using Amoore's Carbinol Threshold Test (Amoore et al., *Rhinology* 21:49–54 (1983)). Thirty-one subjects were able to detect the lowest concentration of 25. Seventeen subjects were able to detect the carbinol smell at the concentration of 55 while the remainder only detected an odor at irritant level.

During the second headache episode, each subject used a pen-like device with the tip impregnated with an odor similar to green apples, a component of the Chicago Smell Test (CST) (A. R. Hirsch et al., *Chemical Senses* 18(5): 570–571 (1993); A. R. Hirsch et al., *Chemical Senses* 17(5): 643 (1992)). Each subject also rated the odor hedonics as positive (pleasant), negative or indifferent (unpleasant). Thirty-five subjects didn't like the odor while fifteen rated the odor (negative) to be positive (pleasant).

The University of Illinois School of Public Health provided the statistical analysis of the data using the t-test for correlation for significant difference from zero and the signed-rank test.

Procedure. After the initial olfactory testing, each subject took a home survey sheet to be filled out during three consecutive migraine attacks. The survey sheet included the name, sex, age, type of headaches and olfactory ability of the subject, and provided a section for rating headache severity on a scale of 1–10.

During the first attack, each subject rated the severity of the headache from 1–10 based on their subjective criteria, with "10" being the most pain and "1" being the least pain that one could theoretically experience. Then they laid in a dark quiet room for ten minutes and rated their headaches again.

During the second episode, each subject laid in a dark quiet room while inhaling the green apple fragrance for ten minutes at their normal respiratory rate. The staff instructed the subjects to hold the pen approximately 2 cm. from their noses. Once again, they rated the headache before and after ten minutes. During the third episode, they rated the headache in the same fashion without the green apple odor.

Results

The results are summarized in Table 1 below. Data for the total group of 50 indicated that the green apple odor did not produce statistically significant improvement in symptoms when compared to just resting in a dark quiet room. However, for the subjects who liked the odor, analysis of their data shows a statistically significant reduction in the severity of their migraines ($p<0.03$).

TABLE 1

						HA #1			HA #2			HA #3		
Pt #	Sex	Age	HA Type	Olf. level	Hedonics	Pre	Post	Delta	Pre	Post	Delta	Pre	Post	Delta
1	f	29	1	25	like (L)	8	8	0	8	6	2	8	8	0
2	f	46	2	25	dislike (D)	7	7	0	8	8	0	7	7	0
3	m	52	3	35	L	10	10	0	10	1	9	1	9	-8
4	m	42	1	25	D	7	7	0	6	2	4	6	5	1
5	f	32	2	25	D	7	7	0	8	8	0	8	8	0
6	f	44	1	25	D	5	5	0	5	2	3	1	1	0
7	f	26	2	25	L	5	1	4	6	0	6	4	1	3
8	f	50	3	25	D	2	0	2	5	0	5	6	1	5
9	m	41	3	55	D	6	5	1	6	7	-1	4	4	0
10	f	33	2	25	D	2	2	0	2	2	0	2	2	0
11	f	37	3	25	D	4	6	-2	3	1	2	4	4	0
12	f	37	2	35	D	3	3	0	3	3	0	3	3	0
13	f	52	2	35	D	4	4	0	2	2	0	2	2	0
14	f	43	2	55	D	1	1	0	2	2	0	2	2	0
15	f	49	1	25	D	5	5	0	5	5	0	5	5	0
16	f	42	2	35	D	4	2	2	7	4	3	3	1	2
17	m	33	1	35	L	8	8	0	8	6	2	8	8	0
18	m	36	1	35	L	6	6	0	4	4	0	8	8	0
19	f	39	2	25	D	2	2	0	2	2	0	2	2	0
20	m	18	1	35	D	10	10	0	9	8	1	9	7	2
21	f	53	3	35	D	7	7	0	8	7	1	8	8	0
22	m	34	3	35	D	4	3	1	3	4	-1	3	3	0
23	m	46	4	25	D	7	7	0	7	7	0	7	7	0
24	f	40	4	25	D	4	4	0	3	3	0	3	3	0
25	f	46	1,4	25	D	4	4	0	3	3	0	5	5	0
26	m	32	1	25	L	8	6	2	10	6	4	7	5	2
27	f	53	1	25	L	10	8	2	10	5	5	10	8	2
28	f	49	5	25	L	4	4	0	5	5	0	5	5	0
29	f	45	3	25	D	8	7	1	7	5	2	8	7	1
30	f	21	6	25	L	4	4	0	4	3	1	3	3	0
31	f	34	1	25	D	8	3	5	10	7	3	10	5	5
32	f	25	1	25	D	5	7	-2	3	5	-2	3	2	1
33	m	33	1	25	L	7	8	-1	8	8	0	8	5	3
34	f	31	1	25	D	7	7	0	7	8	-1	6	5	1
35	m	28	1	25	D	8	8	0	7	5	2	8	8	0
36	f	46	2	35	L	10	9	1	10	4	6	9	9	0
37	f	32	3	25	L	9	9	0	9	10	-1	9	9	0
38	m	55	1	25	D	8	8	0	8	9	-1	8	8	0
39	m	38	1	35	D	7	7.5	-.5	5	6.25	-1.2	5.5	5.5	0
40	f	58	3	35	L	1	1	0	1	1	0	2	2	0
41	f	27	2	35	D	5	7	-2	7	9	-2	7	7	0
42	f	20	2,4	25	D	6	5	-1	7	7	0	7	7	0
43	f	21	1	25	D	7	6	1	7	8	-1	8	6	2
44	m	67	7	35	D	0	0	0	0	0	0	0	0	0
45	m	25	1	35	D	4	4	0	6	4	2	5	5	0
46	f	31	3	35	D	5	5	0	4	5	-1	6	6	0
47	f	34	2	25	D	5	3	2	5	7	-2	3	3	0
48	f	46	4,5	25	L	8	8	0	5	4	1	9	9	0
49	m	18	1	35	L	8	4	2	8	2	6	8	5	3
50	m	37	2,4	25	D	3	5	-2	3	3	0	7	7	0

Headache Types:
1-Traumatic, 2-Common Migraine, 3-Atypical Cephalagia, 4-Muscle Contraction, 5-Costens, 6-Pseudomotor Cerebri, 7-TCE HA, 8-Mixed HA Types.
Positive Delta number indicates improvement in symptoms.

Discussion

The results of this study have great implications for new methods of empiric therapy for migraines. Blau suggests that the eating patterns of the migraine patients in his survey implies that migraine headaches may be triggered in part by deficiency of metabolites. However, the main discussion centers around the therapeutic implications of the survey results. If patients are able to tolerate eating, they should be encouraged to eat starchy foods with their headache medications (Blau, J. N., *Cephalalgia* 13 (1993): 293–295). Blau overlooks the possibility that the positive effects of food is from the odors that are derived therefrom, as 90% of taste is really smell.

The efficacy of the green apple odor in this study hinged upon hedonics. Those patients who like the smell had a statistically significant reduction in the severity of their headaches while those patients who disliked the smell were not significantly affected by the odor in either a positive or negative manner. Similar hedonically linked effects of odor have been demonstrated in regard to learning ability, obesity, claustrophobia, and evaluation of environmental objects. It has been shown that there is a higher prevalence of hyposmia and anosmia in migraine patients then the general population (Hirsch, Alan R., *Headache* 32 (1992): 233–236). However, there was no distinction in olfactory ability between the two hedonic groups that might link the reduction of migraine symptoms with better olfactory ability.

The positive response in the fifteen patients may have been due to an organic effect of the odor itself or their psychological response to the odor through Pavlovian con-

ditioning. These patients may have associated the green apple odor with a past anxiety- or pain-alleviating experience that could have helped them to relax during their headache episodes. Alternatively, in a study of "olfactory-evoked recall," it was demonstrated that food smells were the most common olfactory triggers of this response, in which people recalled certain past events after smelling a certain odor (Hirsch, A. R., *Chicago Medicine* 98 (May, 1995): 16–19). These were usually pleasant memories and were associated with a positive mood state. Thus, by inducing the sufferer to be in a more positive mood state, the headache may have been less severe since a positive mood state tends to reduce headache. The lack of response from those who didn't like the smell is a strong indication that the response of the patient to the odor was more important than the actual chemical impregnated in the pen-tips, but does not preclude the possibility of a neurophysiologic effect of the odors. Serotonin (5HT), norepinephrine (NE), (-Amino butyric Acid (GABA), and Substance P are all known to be both neurotransmitters within the olfactory bulb, hence effected by odors, and essential modulators of headache including migraine. The odor may have had its pain relieving effect in a venue similar to pharmacologic agents used in the management of headache (such as amitriptyline or Phoschol) by modifying the actual neurotransmitters involved in the pain pathway. An integration may have occurred such that in those with negative hedonics for the odor, such a strong negative mood state was induced that the neurophysiologic effect of the odor was unable to overcome it and thus had no pain alleviating effect.

The therapeutic implications of a green apple odorant and other hedonically pleasant odorants are clear. In addition to the standard medical treatment of migraines, patients can further benefit from effective adjuvant therapy such as eating certain foods or inhaling certain odors. The use of fragrances in treating migraines provides more options in treatment for those who poorly tolerate standard medical therapy.

What is claimed is:

1. A method of alleviating cephalic pain caused by a headache in a person, consisting essentially of:

administering to the person by inhalation, a green apple odorant in an amount and for a time period effective to alleviate the cephalic pain; the odorant being hedonically pleasant to the person; wherein a suprathreshold but non-irritant amount of the odorant is administered.

2. The method according to claim 1, wherein the concentration of the odorant is about 25–55 decismel units.

3. The method of claim 1, wherein the cephalic pain is caused by a migraine headache and composed of a pronounced pain on one side of the head, or a throbbing head pain.

4. The method of claim 1, wherein administering the odorant is effective to further alleviate a symptom selected from the group consisting of a visual aura, nausea, blurring of vision, double vision, sensitivity to light, sensitivity to sound, sensitivity to an odor, and a combination thereof.

5. The method of claim 1, further comprising, prior to the administering the odorant:

evaluating the person for olfactory capacity according to an olfactory threshold test; and

adjusting the concentration of the odorant to provide a suprathreshold level for administration to the person.

6. The method of claim 1, wherein the odor is administered to the person for inhalation for a time period of about 5–15 minutes.

7. The method of claim 1, wherein the odorant is administered to the person while in a prone position.

8. The method of claim 1, wherein the odorant is administered to the person in a sound-reduced room.

9. The method of claim 1, wherein the odorant is administered to the person in a darkened room.

10. A method for screening an odorant substance for alleviating cephalic pain caused by a migraine headache in a person, comprising:

administering to the person, an odorant substance for inhalation;

questioning the person as to whether the odorant is positively or negatively hedonic;

administering to the person by inhalation the hedonically pleasant odorant in an amount and for a time period effective to alleviate the cephalic pain caused by a migraine headache wherein a suprathreshold but non-irritant amount of the odorant is administered;

questioning the person as to the effectiveness of the odorant in alleviating the cephalic pain.

11. The method of claim 10, wherein the hedonically pleasant odorant is administered for a time period of about 5–15 minutes.

12. The method of claim 10, further comprising:

having the person lie down in a prone position during inhalation of the hedonically pleasant odorant.

13. The method of claim 10, further comprising:

administering the hedonically pleasant odorant in a sound-reduced room, a darkened room, or both.

14. The method of claim 10, further comprising, prior to the administering the odorant substance:

evaluating the person for olfactory capacity according to an olfactory threshold test; and

adjusting the concentration of the odorant to provide a suprathreshold but not an irritant amount of the odorant for administration to the person.

15. The method of claim 14, wherein the concentration of an odorant is about 25–55 decismel units.

16. An article of manufacture, comprising, packaged together:

(a) an odorant as recited in claim 1, wherein the green apple odorant when inhaled by a person is effective to alleviate the cephalic pain of a migraine headache; and

(b) instructions for use of the odorant according to the method of claim 1.

17. The article of manufacture according to claim 16, wherein the odorant is packaged within a delivery means selected from the group consisting of a vial, jar, pouch, can, box, bottle, blister pack, and a scratch-and-sniff odor patch containing microcapsules of the odorant.

18. The article of manufacture according to claim 16, wherein the odorant is in a form selected from the group consisting of a cloth scented with the odorant, an aerosol spray, a pump spray, a nasal spray, a liquid or solid form of the odorant contained in a vessel having a cap, a liquid or solid form of the odorant contained in a blister pack, and odorant microcapsules contained in a scratch-and-sniff odor patch.

19. The article of manufacture according to claim 16, wherein the odorant is in the form of a cream or a cologne.

20. The article of manufacture according to claim 16, wherein the odorant is in a liquid form contained in a dispenser.

21. The article of manufacture according to claim 20, wherein the dispenser has a tip impregnated with the odorant.

22. A method of alleviating cephalic pain caused by a headache in a person, consisting essentially of:

administering to the person by inhalation a banana or peppermint odorant in an amount and for a time period effective to alleviate the cephalic pain; the odorant being hedonically pleasant to the person; wherein a suprathreshold but non-irritant amount of the odorant is administered.

23. The method of claim 22, wherein administering the odorant is effective to further alleviate a symptom selected from the group consisting of a visual aura, nausea, blurring of vision, double vision, sensitivity to light, sensitivity to sound, sensitivity to an odor, and a combination thereof.

24. An article of manufacture, comprising, packaged together:

(a) an odorant as recited in claim 22, wherein the odorant when inhaled by a person is effective to alleviate cephalic pain caused by a migraine headache; and

(b) instructions for use of the odorant according to the method of claim 22.

25. The article of manufacture according to claim 24, wherein the odorant is packaged within a delivery means selected from the group consisting of a vial, jar, pouch, can, box, bottle, blister pack, and a scratch-and-sniff odor patch containing microcapsules of the odorant.

26. The article of manufacture according to claim 24, wherein the odorant is in a form selected from the group consisting of a cloth scented with the odorant, an aerosol spray, a pump spray, a nasal spray, a liquid or solid form of the odorant contained in a vessel having a cap, a liquid or solid form of the odorant contained in a blister pack, and odorant microcapsules contained in a scratch-and-sniff odor patch.

27. A method of alleviating cephalic pain caused by a headache in a person, consisting essentially of:

determining the character of an odorant as hedonically pleasant or unpleasant by the person, by administering the odorant to the person by inhalation; and

administering a suprathreshold but non-irritant amount of the hedonistically pleasant odorant to the person, by inhalation for a time period effective to alleviate the cephalic pain.

28. The method of claim 27, wherein the odorant is selected from the group consisting essentially of green apple, banana, and peppermint.

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United States Patent [19]

Burgess

[11] **Patent Number: 4,463,016**

[45] **Date of Patent: Jul. 31, 1984**

[54] **METHOD FOR THE TREATMENT OF RAZOR BUMPS**

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[73] Assignee: **Nel's Laboratory, Inc., Bronx, N.Y.**

[21] Appl. No.: **421,474**

[22] Filed: **Sep. 22, 1982**

[51] **Int. Cl.**[3] **A61K 31/055**

[52] **U.S. Cl.** **424/347**

[58] **Field of Search** 424/347

[56] **References Cited**

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Primary Examiner—Leonard Schenkman
Attorney, Agent, or Firm—James H. Callwood

[57] **ABSTRACT**

The present disclosure is directed to a method of treating razor bumps which comprises administering to an individual suffering from razor bumps an effective amount of a 4-chloro-3,5-diloweralkylphenol compound in combination with a vehicle which facilitates topical application of said 4-chloro-3,5-diloweralkylphenol compound.

6 Claims, No Drawings

METHOD FOR THE TREATMENT OF RAZOR BUMPS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed to a method for the treatment of razor bumps. More particularly, the present invention is directed to a method for treating razor bumps which comprises administering to an individual suffering from razor bumps an effective amount of a 4-chloro-3,5-diloweralkylphenol compound in combination with a vehicle which facilitates topical application.

2. Description of the Prior Art

Pseudofolliculitis of the beard (pseudofolliculitis barbae) more commonly known as "razor bumps" is an inflammatory state of the neck and chin which is characterized by erythematous lesions, firm papules and pustules containing buried hairs. While this affliction is known in Caucasions, it is essentially a condition which, in its most severe manifestations, is peculiar to the Negroid races. Strauss et al.: Pseudofolliculitis of the Beard; Arch. Dermatol (1956); 74:533–542.

The stated condition has been characterized by Strauss et al. supra as stemming from the curvy nature of Negroid hair which, upon growing out of the hair follicle, curves back in an arch and penetrates the skin.

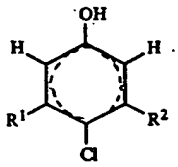
The methodology of treatment disclosed in Strauss et al. suggests the use of depilatories such as barium sulfide powder or calcium thioglycollate for alleviation of symptoms of the condition. Additionally, Strauss et al. suggests that the topical application of such antibacterial agents as tetracycline or petrolatum produced insignificant long-term effects and that little is to be gained by combining antibacterial treatment with the use of depilatories.

One significant disadvantage of the use of depilatories is the fact that because they tend to irritate the skin, they can only be used infrequently by a substantial number of those persons who suffer from pseudofolliculitis, For example, Strauss et al. supra recommends that the depilatory be administered only once every three days to avoid irritation of the skin, and that even with this low frequency of administration, there was an occasional complaint regarding irritation.

For obvious reasons, the use of depilatories once every three days has significant drawbacks. For example, the growth of the beard which occurs during the three-day period could quite possibly cause an unkempt appearance. In accordance with the present invention, a methodology for treating "razor bumps" is described which avoids the problems of infrequent application and irritation associated with the prior art procedures.

SUMMARY OF THE INVENTION

A methodology for the treatment of razor bumps which comprises administering to an individual suffering from razor bumps an effective amount of a compound of the formula



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wherein R^1 and R^2 are C_1–C_7 straight- or branched-chain alkyl,

in combination with a vehicle which facilitates topical application of the compound of formula I.

DETAILED DESCRIPTION OF THE INVENTION

As used throughout the specification and the appended claims, the term "alkyl" denotes a C_1–C_7 aliphatic hydrocarbon radical which may be straight- or branched-chain. Exemplary of alkyl are methyl, ethyl, propyl, isopropyl, butyl, secondary butyl, tertiary butyl, aryl, hexyl, heptyl and the like. The foregoing list of designations of alkyl is intended merely to provide exemplification and is intended to be non-limiting. The term "razor bumps" denotes the condition known as pseudofolliculitis barbae which is an inflammatory state of the neck, chin and jowl characterized by erythematous lesions, firm papules and pustules containing "buried" or "ingrown" hairs. It is recognized that the term "razor bumps" can also include other forms of pseudofolliculitis such as pseudofolliculitis capitae.

The compound of formula I may be administered to the chin, neck and jowl for the treatment of "razor bumps" in the form of a cream or a salve. Such a cream or salve would preferably contain the compound of formula I in concentrations in the range of from about 0.5% to 4.0% by weight of a compound of formula I in combination with a vehicle to make up a composition for topical application. Such a composition, in addition to containing an effective amount of a compound of formula I, would also preferably contain the following:

- Purified or distilled water;
- A moisturizing agent for retaining the water in the composition. Exemplary of a suitable moisturizing agent is propylene glycol;
- A skin lubricant, e.g., lanolin;
- A settling agent, e.g., sodium stearate;
- A skin moisturizing agent, e.g., polyethylene glycol monostearate;
- A skin lubricant such as sesame oil;
- A skin moisturizer such as cetyl alcohol;
- Antibacterial agents such as methyl benzoate and propyl benzoate;
- An aseptic and anti-irritant agent such as camphor; and
- A fragrance such as cucumber fragrance No. 24.

A preferred range of the compound of formula I in an antirazor bump composition is about 1.0% to 3.0% by weight, most preferably about 1.5% by weight.

Among the compounds generically encompassed by formula I, the compound 4-chloro-3,5-dimethylphenol (Entry No. 2165, Merck Index, 9th Edition) is most preferred as the active ingredient.

The invention is further exemplified by the following examples:

EXAMPLE I

Formulation Procedure

1. Place propylene glycol and purified water in a container and heat to 90° C. Then, dissolve sodium stearate and lanolin in appropriate proportions into solution.

2. In a separate container, add polyethylene glycol monostearate, 4-chloro-3,5-dimethylphenol, cetyl alcohol, methyl and propyl paraben, camphor and sesame oil. Heat to 170° F. Add fragrance.

Add "1." to "2." and mix well. Cool to 125° F. to 135° F. and fill in specified containers.

EXAMPLE II

1.5% Formulation

Percent		Weight
35.0	Propylene Glycol	39.61 kg
31.0	Purified Water	35.21 kg
15.0	Lanolin	17.00 kg
11.0	Sodium Stearate	12.50 kg
2.0	Polyethylene Glycol Monostearate	2.30 kg
2.0	Sesame Oil	2.30 kg
1.5	4-Chloro-3,5-Dimethylphenol	1.70 kg
.5	Methyl Paraben	.568 kg
.2	Propyl Paraben	.230 kg
.2	Camphor	.230 kg
.5	Cucumber Fragrance	.568 kg
1.1	Cetyl Alcohol	1.42 kg

EXAMPLE III

2.0% Formulation

Percent		Weight
2.0	4-Chloro-3,5-Dimethylphenol	2.26 kg
30.75	Purified Water	34.92 kg
14.75	Lanolin	16.71 kg
35.0	Propylene Glycol	39.61 kg
11.0	Sodium Stearate	12.50 kg
2.0	Polyethylene Glycol Monostearate	2.30 kg
2.0	Sesame Oil	2.30 kg
.5	Methyl Paraben	.568 kg
.2	Propyl Paraben	.230 kg
.2	Camphor	.230 kg
.5	Cucumber Fragrance	.568 kg
1.1	Cetyl Alcohol	1.42 kg

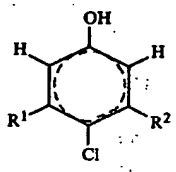
EXAMPLE IV

3.0% Formulation

Percent		Weight
3.0	4-Chloro-3,5-Dimethylphenol	3.40 kg
30.25	Purified Water	34.23 kg
14.25	Lanolin	16.15 kg
35.0	Propylene Glycol	39.61 kg
11.0	Sodium Stearate	12.50 kg
2.0	Polyethylene Glycol Monostearate	2.30 kg
2.0	Sesame Oil	2.30 kg
.5	Methyl Paraben	.568 kg
.2	Propyl Paraben	.230 kg
.2	Camphor	.230 kg
.5	Cucumber Fragrance	.568 kg
1.1	Cetyl Alcohol	1.42 kg

What is claimed is:

1. A method for the treatment of razor bumps which comprises topically administering to an individual suffering from razor bumps an effective amount of a compound of the Formula:



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wherein R^1 and R^2 are C_1–C_7 alkyl in combination with a vehicle which facilitates topical application of the compound of Formula I.

2. The method according to claim 1 wherein R^1 and R^2 are methyl.

3. The method according to claim 2 wherein said effective amount of a compound of formula I is in the range of about 1.0% to 3.0% by weight.

4. The method according to claim 1 wherein said effective amount of a compound of formula I is in the range of about 1.0% to 3.0% by weight.

5. The method according to claim 4 wherein said effective amount of a compound of formula I is about 1.5% by weight.

6. The method according to claim 5 wherein said vehicle is composed of ingredients selected from the group consisting of propylene glycol, purified water, lanolin, sodium stearate, polyethylene glycol monostearate, sesame oil, cetyl alcohol, methyl paraben, propyl paraben, camphor and cucumber fragrance.

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